CLINICAL ALLERGY

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A Practical Guide to Diagnosis and Treatment

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Preface to Second Edition

The first edition of this book appeared in 1945 In the preface, I stated the necessity for a concise volume devoted to clarifying the field of allergy for the general practitioner and medical student. Since that time the literature has become even more voluminous and controversial so that the need for a simple guide to the subject has increased rather than diminished Various chapters in the second edition have been enlarged to bring to the attention of students and practitioners the new material accumulated during the past six years In keeping with the effort to make available a compact, practical manual only essential references have been included The reader is referred to longer reference works for more comprehensive bibliographies

Special immunologic phenomena are described, such as the thermostable antibody, reverse passive transfer, and inverse anaphylaxis Their clinical significance in allergic practice has been pointed out The various antihistaminic drugs used in practice with their indications and dosage are included The use of ACTH and Cortisone, particularly in chronic intractable asthma, is described. Chapter XI, Miscellaneous Allergic Conditions includes gastrointestinal allergy, allergic purpuras allergy of the eyes migraine and allergic headache, allergic arthritis genitourinary tract allergies, cardiovascular allergy, hypertension, physical allergy, and periarteritis nodosa.

I have made every effort to avoid theory and controversy and technical details of interest only to the specialist. It is hoped that this handbook will continue to provide the general physician with a clear, simple and accurate guide to effective diagnostic and therapeutic measures that he can readily apply in his own practice

I am deeply grateful to my secretary and technician Miss Barbara A Winder, B.S for the invaluable assistance rendered in the preparation of this book, and to my son Robert G Taub B S, M D for his assistance in the revision of the chapters on physiology of respiration and immunology

Chicago, Illinois S J T

CLINICAL ALLERGY

Chapter I

Introduction

ALLERGY AND INTERNAL MEDICINE

A broad general knowledge of internal medicine is the first essential to the diagnosis and evaluation of an allergic condition

The various forms of allergy are so diverse in their clinical symptomatology that almost every specialty in medicine is represented, such as otolaryngology, dermatology cardiology, ophthalmology, pediatrics and even surgery

Therefore, in every case a complete history must be taken and physical examination and routine laboratory studies made Physical examination of the chest may disclose an early bronchogenic carcinoma of the lung whose only symptom is an asthmatic wheeze a complete history with dates of onset of symptoms may reveal a seasonal hay fever routine stool examination in a patient with urticaria may show intestinal parasites careful physical examination may disclose cardiac dyspnea which may simulate bronchial asthma

The point to be emphasized is that the study of allergy is not a laboratory science but a specialty of clinical medicine in which all the diagnostic aids of medicine are to be utilized

PREVALENCE AND INCIDENCE OF ALLERGY

It is no exaggeration to state that 50 per cent of all people have at some time in their lives some manifestations of allergy The symptoms may be an eczema in early childhood an occasional urticaria a rhinitis serum sickness a gastrointestinal disturbance or an adverse reaction following the use of some simple drug

About 10 per cent of the general population have some obvious manifestation of allergy in one or more of its forms It is estimated that 20 per cent of the population have some type of hay fever, 40 per cent of whom eventually develop bronchial asthma

The age incidence of allergy is as follows

Infants Cyclic vomiting may be one of the earliest manifestations of a food sensitivity infantile eczema may also appear early due to numerous sensitivities Hay fever and asthma likewise occur commonly in this group

Young children In the past few years hay fever and asthma have become more prominent in this age group

Adolescents and adults It is very common to obtain a history of some previous allergic disturbance and it is apparent that in this age group a blossoming out of previously subclinical allergy may occur

There is no essential difference in either sex or race relative to the incidence of allergy

HEREDITY

It has been established that 70 per cent of all cases of allergy show a family history of this condition The correct conclusion to be drawn from this high family incidence is that these people have probably inherited a capacity to develop sensitivities that do not arise in normal people *The underlying cause of the allergic state is not known* Exactly what is transmitted through the genes in an allergic person is not clear however, such an individual inherits the predisposition to manufacture antibodies against substances not antigenic to the normal individual

The importance of an antecedent history of allergy lies in the fact that allergic manifestations may be expected at an earlier age than otherwise For example, overindulgence on the part of pregnant women in certain protein foods such as milk or eggs may result in a leakage of this protein through the gastrointestinal tract into the blood stream and thence through the placenta to the fetus In a potentially allergic fetus this may result in the manufacture of antibodies to this protein by the fetus so that later in life when the child is first fed this protein allergic symptoms develop immediately This is offered in explanation of the often noted clinical finding of allergic symptoms after the first feeding

The type of sensitivity displayed by one member of a family bears no relationship to the type developed by another member, for example a father may have bronchial asthma and the child may have hay fever or migraine Nor does the marriage of two allergic individuals necessarily guarantee a more severe type of allergy in the offspring however, it does mean that the appearance of an allergy in the offspring will probably occur at an earlier age Where only one parent is allergic, the chance of the offspring showing allergy is much less than where both parents suffer from the condition

Chapter II

Immunochemistry and Its Relation to Clinical Allergy

The study of allergy has become widespread only since 1920 The recognition of and scientific approach to the problem of hyper sensitivity began long before, around 1900, at the same time that great advances were being made in immunology The two major discoveries which led to a recognition of allergic phenomena were the discovery of anaphylaxis and the development of immune sera for the treatment of various diseases

It was found that a foreign protein injected into an animal s body led to the production of specific agents against this intruder which could remove it by precipitation or agglutination When the work of the late nineteenth century showed that many of the toxins found in nature were protein substances investigators began to ascertain their immunologic properties It was first shown that snake venom when injected in sublethal doses into a pigeon led to the production of substances in the bird s blood which specifically neutralized this toxin A normal animal could be protected against an ordinarily lethal dose of snake venom by being treated soon after exposure with serum from a pigeon immunized against this venom This anti toxin treatment was next applied to bacterial diseases where the predominant pathologic effect was due to the elaboration of a potent exotoxin by the organism

In 1891, von Behring was able to announce the sensational news

that diphtheria could be cured in what would have previously been fatal cases by the use of immune sera Thus the era of serum therapy was initiated and for the first time large quantities of foreign protein material were being routinely administered to human beings As this mode of therapy became more general it was noted with increasing frequency that severe reactions could follow the administration of this healing serum The nature of the symptoms observed will be discussed more fully in Chapter XII on serum sickness

These reactions were not entirely new phenomena Scientists had noted them previously in immunologic studies on animals and in the administration of foreign blood to humans but since the latter practice had never been widespread the problem was never serious and remained a laboratory topic However in 1902 Richet was able to clearly describe a procedure by which injected foreign protein could be made dangerous to an individual If a foreign protein was injected and a suitable interval allowed to elapse the subsequent readministration of this protein led to a severe constitutional reaction which often terminated in death The first dose sensitized the animal the second led to severe physiologic maladjustments However if the animal recovered no permanent harm appeared to have been done This process was called anaphylaxis

At first no similarity between this phenomenon and serum sickness was recognized because of the relative mildness of the second condition However in 1905 Pirquet and Schick published their discussion of serum sickness in which they definitely drew a parallel between this condition and anaphylaxis They believed that serum sickness like anaphylaxis resulted from an antibody antigen reaction and that the dose of serum given was both the sensitizing and shocking dose The accelerated and intensified reactions often obtained upon reinjection of the serum were believed by them to be due to a change in the individual caused by the primary injection and were called allergic or altered reactions This work laid the basis for the investigation of the whole field of hypersensitivity phenomena Extensions of its concepts to the fields of pollen and food allergy syndromes which had been previously known but not too well understood led to the development of allergy as we know it today

THE IMMUNOLOGIC MECHANISM

In this chapter we shall briefly review the mechanism of the ordinary types of immunologic reactions with special reference to similar phenomena in allergy The next chapter will concern itself with a more thorough discussion of the unique characteristics and the anaphylactic and allergic response It is certainly not necessary to apologize for including a discussion of immunochemistry in a book on allergy The importance of these concepts in the development of the field has been noted above When the nature of the allergic phenomenon is discussed this close interrelationship between immunology and allergy will become even clearer Because many of the readers of this book will have been away from their didactic work on immunology for a long enough period to make the subject a bit hazy we feel that a short review will be of considerable value in facilitating clear understanding of the material on hypersensitivity which follows

The basic mechanism of the immunologic reaction is as follows A foreign protein called the antigen is injected into an animal After a suitable time the animal responds with the production of specific proteins which appear in its blood stream and which are capable of neutralizing the antigen These bodies are called antibodies When an antigen is brought into contact with a specific antibody a reaction occurs whose character is dependent upon the nature of the antigen While the antibody produced may be a lysin precipitin opsonin agglutinin or antitoxin the basic mechanism underlying the production of these various antibodies is identical and one immunologically pure antibody may have several different functions such as being both a precipitin and an agglutinin

The events outlined above will now be considered in more detail We shall first consider what characteristics proteins possess which cause the production of antibodies specific for them the nature of antigens the nature and mode of formation of antibodies and the characteristics of antibody antigen reaction

The Structure of Proteins

Proteins are complex substances of high molecular weight composed mainly of amino acids with peptide linkages Proteins can

differ from each other both in the type and the proportions of their constituent amino acids This in itself would permit a tremendous number of different proteins to be formed But there is another structural difference of great importance in immunology This is the type of spatial configuration which the protein may adopt Proteins do not exist only as extended amino acid chains but roll up in a very specific way, the nature of which is due in part to the arrangement of the constitutent amino acids For example, two proteins can be virtually identical with respect to their amino acid constitution and arrangement and yet, because of differences in the way in which they fold, show large immunologic differences This is also the reason why a denatured protein will differ from its native protein to such an extent that no cross reactions can be observed The denatured protein is practically identical to the native protein as far as amino acid composition and arrangement are concerned, but it has unrolled and is thereby markedly changed in its spatial configuration This fact is used extensively in allergy For example, procedures have been developed to make therapeutic sera less specific by denaturing as much as possible all extraneous protein while retaining the potency of the antitoxin In the very severe milk allergies of children success in treatment can sometimes be obtained by feeding evaporated milk in which heating has destroyed the immunologic character of the milk proteins while still retaining their nutritive value

While we have confined our discussion to the effect of protein configuration on the antigenicity of proteins, it should be noted that the same considerations hold for antibodies Antibodies seem to be normal constituents of the serum protein which have been slightly altered so as to possess immunologic activity toward specific proteins It seems probable that the major alteration which they undergo is a change in the pattern of the folded state To bring out these points more clearly, the nature of the antigens and antibodies will be considered

The Nature of Antigens

Antigens are always large molecules their molecular weights beginning at about 10 000 Consequently they are all of colloidal nature This is of practical importance, since many compounds which are only weakly antigenic can be made stronger when adsorbed

onto colloidal substances Nearly all antigens are protein although some carbohydrates of high molecular weight will form specific antibodies when injected alone Proteins show considerable variation in their antigenicity with a correlation between size and antigenic power

As has been noted above the antigenicity of proteins depends upon both their chemical composition and their spatial configuration However the molecule as a whole does not act as the directive element in the formation of antibodies only specific portions upon its surface are involved These active groupings act as the templates upon which the specific antibodies are formed The more similar antigenic proteins are chemically the more tendency there will be *for their more active groupings to be similar This will lead to immunologic cross reactions between them This has also been shown to be true with the carbohydrate antigens These active groups are probably not identical even in the same protein molecule* As would be expected the number of active groups on a protein molecule depends upon its size—the larger the molecule the more groups it contains

The immunologic specificity of antigens can be altered by a variety of procedures such as denaturation oxidation reduction deamination formaldehyde treatment esterification etc The alteration in specificity obtained when various chemical groups are put into the protein molecule will be discussed under haptens Normal proteins show a certain parallelism in their antigenicity Proteins from different organs of the body are very different immunologically but in closely related species proteins serving the same functions are very similar as antigens This is believed to be due to the close chemical similarity existing between them and has been used *in working out the phylogenetic relationships between various animals the extent of cross reactions between them indicating the closeness between species*

It might also be briefly mentioned that various bacterial animal and plant toxins have been shown to be proteins and antisera against many have been prepared

The Nature of Antibodies

Antibodies are serum proteins and are found in the globulin fraction The active immunization of an animal calls forth considerable

increase in its blood globulin content and a change in the albumin-globulin ratio ensues. The serum globulin is not homogeneous but [illegible] The [illegible] d, or [illegible] the [illegible] al is treated with specific antigen, the precipitate removed, and the serum analyzed, it is found that the gamma globulin fraction has been markedly decreased. Consequently, the major difference between normal globulin and antibody seems to reside in their relative configurations. Further evidence for this is the fact that the antibodies can be functionally destroyed by denaturation, acid, formaldehyde, etc., all agents which alter the configuration or chemical nature of the antibody molecule.

The site of antibody formation is still not completely determined. Since, on the whole, they seem to be normal serum proteins, it would seem probable that they were formed in the normal site for blood protein formation. This has recently been shown to be the liver. However, it is believed that immune bodies are formed not only here but in the whole of the reticulo-endothelial system. This question is of special importance in allergy since the degree of sensitization obtained depends in part upon the way in which the antigen is administered. There are some suggestive data indicating that antibody formation may occur in connective tissue cells anywhere in the body.

Antibodies appear in the blood within a few days after the injection of an antigen and reach their maximum number within a week. However, a rapid decline soon results unless further antigen is administered. A very high titer of antibody can be obtained in the blood by the continuous injection of antigen but eventually a level is reached where further administration of the foreign protein has no effect. However, even in these cases a gradual reduction in the antibody titer results after the antigen injection is stopped.

If sufficient time elapses, the antibody content of the blood may decline to zero. However, subsequent administration of the previous antigen calls forth an increase in antibody titer which is far more rapid and extensive than that produced by the original injection. This is called the anamnestic reaction. The cells of the reticulo-endothelial system seem to retain the ability to make the specific antibody to which they were sensitized and respond very promptly and mark-

edly to the new stimulating dose Related antigens bring forth as extensive a response as the original antigen although evidence has been presented that the injection of a nonrelated protein can cause the accelerated production of antibodies which the animal had manufactured as a result of previous immunization procedures This is of special importance in allergic phenomena It has been used in hyposensitizing individuals to pollens After a year of perennial treatment the patients are given booster doses of pollen just before the season to call forth by anamnestic reaction sufficient protective antibody to carry them comfortably through the season An allergic patient subject to multiple sensitivities will often show an excessive reaction to all offending allergens when severely exposed to one of them Patients continually exposed to an offending allergen show increasingly severe symptoms which may be in part due to an anamnestic increase in the reagin content of the body

There are two theories of antibody formation both of which are probably partly true The first step in antibody formation is an incorporation of the antigen into the cells of the reticulo endothelial system This calls forth an increased production of globulin One theory believes that the presence of the antigen causes the globulin molecules forming in its neighborhood to alter slightly so as to mirror parts of the active group of the antigen molecule These specialized parts of the antibody molecule are the functional groups participating in the antibody antigen reaction

The other theory places emphasis upon what happens to the globulin after it is formed The ends of the amino acid chain of which the protein is composed are supposed to unroll and lose their specificity and then reroll in the presence of the antigen These rerolled ends having been reformed upon the template of the antigen mirror parts of its surface and are able to combine with it

These theories explain the specificity of immunologic reaction since the active antibody formed corresponds to a great extent to the reverse of the antigen and will react only with a molecule having the antigen s configuration Another important point is the fact that there are a number of active points on the antigen s surface all of which differ in some way from each other Antibodies formed upon different active points will not be identical Furthermore the antibody may form upon only part of the template or may take an in

complete impression Consequently the antibodies formed to the injection of a pure antigen are not homogeneous with respect to their spatial configuration but show many variations The differences between antibody molecules are so small that no chemical fractionations of homogeneous antibody can be done but variations in the reactivity of antibody fractions have been noted in haptenic reactions

The above mechanism also explains cross reactions When an animal is immunized to a protein such as egg albumin the addition of a closely related protein such as duck albumin to the immune serum causes formation of a precipitate which while considerable in magnitude is not as heavy as that obtained when egg albumin is added Addition of a more distant protein such as dog albumin would at most call forth only a very slight response while if an unrelated protein were administered (e g horse globulin) no reaction at all would be elicited These cross reactions are very important in allergy Patients with food and pollen sensitivities frequently show an allergic response to many or all allergens of a botanical or phylogenetic group The basis for cross reactions is the fact that in similar proteins from closely related species the chemical composition and consequently the active points of the proteins are so similar that antibodies formed on one protein s template will find sufficient similarity in that of another to form a stable linkage The more distant the species the less identical its active points will be with those of the immunizing protein Cross reactions bring up the question of the nature of the antibody antigen combination and we shall briefly consider this next

The Antigen Antibody Combination

The nature of the antigen antibody combination is one of the most complex and controversial features of immunochemistry However a number of basic facts have been determined The reaction between an antibody and its causative antigen is very specific cross reactions appearing only under the circumstances detailed above This combination is a chemical one which involves entire molecules and not split products Both antibody and antigen enter into the specific complex the molecules being held together by forces existing at their surfaces No alteration in the chemical nature of antigen or

antibody results from this combination, and although the molecules are held together firmly it is possible to partly reverse the aggregative reaction and obtain the components in an unchanged condition. Antibody and antigen can combine in varying proportions but the explanations for this will not be considered here.

There are two stages to the normal serologic reaction. There is first a preliminary combination between antibody and antigen leading to complex formation. Next, these complexes aggregate, leading to precipitation or agglutination, or else initiate the chemical events leading to lysis. The first stage is the important one in allergy, the allergen combining with a fixed antibody to initiate the allergic reaction. Two more aspects of immunochemistry will be considered and we shall then turn our attention to anaphylaxis and allergy. One topic, the nature of the haptens, has direct applications in drug allergy while our other topic, complement fixation, is included because it may have a significance in allergy which is not at present recognized.

The Nature of Haptens

The work discussed above has shown that the specificity of a protein antigen is due to the presence on its surface of active points which the forming antibody uses as templates. If these active points could be altered in a specific manner, a new antigen would be produced whose nature could be controlled. This has been possible through the use of haptens. A hapten is a substance, generally an organic compound of low molecular weight, which when combined with a protein so alters its immunologic specificity that antibodies formed in response to administration of the conjugated protein are specific for the new prosthetic group and are not at all characteristic for the protein component. Any protein coupled with this hapten will show a maximal precipitate when added to the anti-hapten serum. However, this anti-hapten serum is specific for the one particular hapten which stimulated its formation and will not react with proteins combined with other chemical compounds, although cross reactions are observed even with these altered proteins. When the haptens are chemically related there is a considerable degree of cross reaction. Haptens themselves cannot induce the formation of specific antibodies but once these have been formed, the hapten alone can com-

bine with them No precipitation occurs in this case unless the hapten is very large Certain haptens only partially alter the active points of a protein molecule This is the case when treatments such as methyl ation acetylation iodination bromination etc are used Since these haptens only partially change the character of the antigen antibodies which form after its administration are specific both for the protein and the hapten

The Role of Complement

Complement is a protein substance found in the globulin fraction of serum It is required for the completion of certain serologic reac tions especially those involving bactericidal and hemolytic reactions In these the antigen antibody combination requires the incorpora tion of complement before the characteristic reaction appears Com plement may function in some phases of bacterial and possibly other types of allergy but there is no evidence for this Complement fixa tion is also one of the better tests for showing the presence of specific antibodies and as such has been used in allergic research Other tests which have been used are the precipitin reaction passive sensitiza tion and antigen neutralization The last two tests will be described in more detail in the next chapter which deals with anaphylaxis and allergy

SPECIAL IMMUNOLOGIC PHENOMENA

The *thermostable or blocking antibody* is demonstrated by heating the serum to 60° C for one hour The antibody produced by this process is protective in nature and follows repeated injections of [illegible] be demonstrated in cases [illegible] doses of a pollen extract [illegible] equal amounts of the blocking antibody and the antigen or pollen extract are added no reaction occurs when injected intra dermally in a pollen sensitive patient The blocking antibody has been shown to be a specific precipitin reaction

Reverse passive transfer is demonstrated by injecting a large dose of an antigen into a normal animal Shortly afterward a dose of sen sitized serum is injected An anaphylactic reaction occurs sooner than in the normal type of passive sensitization This type of reaction is analogous in the human to the reactions that occur in blood trans

fusion when the donor is allergic to a food pollen or epidermal substance and the recipient either eats the particular food such as egg white milk or wheat or is exposed to the pollen or epidermal substance and symptoms of asthma urticaria or hay fever may occur Symptoms have persisted from a few days to as long as six months but they are not permanent and eventually completely disappear

Inverse anaphylaxis is the phenomenon produced by injecting rabbits three times weekly with guinea pig serum The rabbits are bled at the end of four weeks and the serum is injected intracardially into guinea pigs with resulting death in anaphylactic shock

The *Forssman antibody* is demonstrated by injecting rabbits with a suspension of sheep s cell producing anti sheep s cell rabbit serum This is injected intracardially in a guinea pig with resulting anaphylactic death

Some antibody molecules form precipitates with the antigen whereas others combine with the antigen to form soluble complexes In human hypersensitivity the complexes are the soluble type In immune states the complexes form precipitates

THE IMMUNOCHEMICAL MECHANISM INVOLVED IN ALLERGY

The exact nature of the production of the allergic reaction is not known

Abramson points out that the histamine theory rests primarily on biologic assay in which the assumption is made without proof that histamine is the offending substance Campbell further questions this hypothesis and points out that B acetylcholine histamine or other histamine like substances may be responsible for the varied manifestations of the allergic state Because of the rapidity of their action on experimental animals he assumes the effect to take place on the nerve mechanism of the cells Boyd is also noncommittal in his recognition of the toxic agent and groups these substances as histamine like substances

Bronfenbrenner s hypothesis on the antigen antibody reaction in which he postulates the action of proteasis is not completely accepted He too is vague as to the substance which is responsible for allergies in man whether it be the peptones which cause the release of histamine or histamine like substances or the liberation of an

enzyme which in turn affects liberation of preformed histamine
F
c

the human and its end products remain in a controversial state

THE ROLE OF THE PITUITARY ADRENAL CORTICAL SYSTEM IN IMMUNITY

The role of the adrenal cortex in immunity has recently been shown to be of some importance * It has been shown that injection of ACTH or certain adrenal cortical steroids (11 oxysteroids) causes a dissolution and degeneration of lymphocytes and a resultant de crease in the lymphoid tissue of the body Although the site of anti body formation has not been definitely determined it is known that in immunized animals one of the constituents of the lymphocytes is antibody globulin Furthermore it has been shown that the circulat ing antibody titer increases in a previously immunized animal with
d These results
in the pituitary
oid tissue in the
than the normal
quantity of ACTH when the body is exposed to a wide variety of stresses and this may explain the anamnestic reaction which is caused by so many varied stimuli Almost any type of antigen when intro duced into the body augments pituitary secretion and hence adrenal cortical secretion and this may be responsible for an anamnestic type of reaction

Increased amounts of circulating adrenal cortical steroids also cause a substantial increase in the number of macrophages in the tissues This increase in the number of macrophages increases the phagocytic capacity of the reticulo endothelial system

It has been further shown that hyaluronidase is inhibited by adrenal cortical extracts This suggests that the adrenal cortical steroids may play an important part in maintaining the ground sub

* See A. White The role of the adrenal cortex n mmun ty *J Allergy* 2 275 1950

secretion causes a disappearance of blood eosinophils but the mechanism by which they ameliorate the hypersensitive state is not clear as yet. At the present time it appears paradoxical that adrenal cortical steroids should increase the amount of circulating and tissue antibody and yet alleviate the hypersensitive state.

Chapter III

The Dynamics of Allergy

ANAPHYLAXIS AND ALLERGY

The processes of anaphylaxis and allergy differ from the reactions considered in the previous chapter mainly in the way in which they

of only a few days If after one or several initial or sensitizing injections of antigen the next injection is withheld for a period of two

from a sensitized individual to a nonsensitive one, the recipient retaining his altered reactivity for several weeks.

because of the differences observed. Coca has put forward the concept of atopic diseases, by which he means those conditions caused [illegible] sensitivity This is contrasted with the non-

[illegible] esult of repeated contact
[illegible] emonstrated between the
[illegible] reside in the strength of

the hereditary predisposition As the discussion below will demonstrate, the major way in which allergy differs from anaphylaxis is not

in the fundamental pattern of its ... way responses

directly introduced into the body :

An allergic patient reacts in a much more sensitive manner. He will show responses when the allergen is brought in contact with his nasal mucosa, skin, gastrointestinal tract, lungs, or eyes. It is this ability to respond to direct superficial contact with the allergen and the localization of the reaction in one or several specific tissues that differentiates the allergic from the anaphylactic. A further important difference is the fact that while the anaphylactically sensitized animal shows both circulating precipitins and the ability to passively sensitize other animals, the sensitizing antibodies or reagins of the allergic patient are so tightly bound to cellular structures that they appear in the blood stream in a quantity too small to cause generalized passive sensitization in a normal individual and do not yield a precipitin reaction.

However, there are *also* points of *similarity* between anaphylaxis and allergy. Both are immunologic reactions. The inadvertent administration of allergen either in excessive amounts or intravenously causes a response which is identical with the anaphylactic reaction of animals. Furthermore, even the milder responses of the allergic patient mimic the more acute events in an anaphylactically shocked animal. One of the best indications of the essential unity of allergy and anaphylaxis is shown by serum sickness. In the normal serum sickness reaction, symptoms appear after about six days, and reach a peak at twelve days. At the same time precipitins to the injected serum appear in the blood. The symptoms are relatively mild and are believed due to the production of sensitizing antibodies concomitantly with the precipitins which then react with antigen still remaining in the body. This is a mild anaphylactic reaction. Its ... r the

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an accelerated reaction may occur, the symptoms appearing after three to five days and being mild or severe, depending upon the sensitivity of the patient and upon the amount of serum injected. Nonsensitive patients may show only primary serum sickness upon

reinjection with the normal incubation period of from six to twelve days.

The accelerated reaction is due no doubt to the presence of sensitizing antibodies or reagins fixed to tissue cells from the previous exposure and to their more rapid and prolific production after reintroduction of the serum due to an anamnestic reaction. Thus the [illegible] e plenty of circulating [illegible] apid and in many cases [illegible] designated by Coca as having nonatopic allergy, since they derive their sensitivity from a previous exposure. Precipitins are also found in these individuals. However, the inherent sensitivity of the individual is the determinant factor in producing the type of response. Some individuals show an immediate reaction upon readministration of serum. The closer in time the primary and second injection are, the more immediate will be the reaction shown by a sensitive individual. This type of response is generally extremely violent and may reach the [illegible] within twenty-four hours. [illegible] ction upon administration [illegible] riably suffering from a simultaneous allergy to the protein of the animal whose serum was used. Patients suffering from asthma due to horse dander give very severe responses with horse serum. The immediate reaction is due to a very high content of specific reagins chronically present in the individual's tissues. This type of response is termed by Coca a true atopic reaction.

Before considering the mechanism of the hypersensitive reaction, we might recapitulate some of the evidence which shows the immunologic character of the anaphylactic and allergic reactions. We have already shown how close the ties were between the experimental [illegible]

sickness, and more directly in other allergic conditions. This again is typical of immunologic phenomena. Another similarity is the fact that an initial exposure must occur before individuals exhibit hyper-

sensitivity This is very clear cut in anaphylaxis and serum sickness and is also true of even atopic hypersensitivity

MECHANISM OF THE HYPERSENSITIVE REACTION

The development of a hypersensitive individual or animal occurs in a well-defined sequence The individual is first exposed to a foreign protein which causes the production of specific antibodies Some of the antibodies produced have the ability to combine with tissue cells and sensitize them Upon readministration of the antigen an antibody antigen combination occurs upon the surface of the sensitized cells leading either to the formation of a powerful chemical substance (H substance) or to a functional repercussion on the part of the affected cell The H substance or altered cell causes the profound effects observed

Effect of Exposure to a Foreign Protein

The genesis of the hypersensitive state will be considered separately for anaphylaxis and allergy Experiments have shown that in anaphylaxis previous exposure to an antigen must occur before a condition of sensitivity sets in The evidence that this reaction is produced by an immunologic type of response is quite extensive The animal is not immediately sensitized but an incubation period of about two weeks must be allowed to elapse before a dose sufficient to cause anaphylaxis can be administered During this period the antibody content of the blood gradually increases in amount while at the same time the animal becomes increasingly sensitive This circulating antibody is specific for the injected antigen and will give precipitin reactions and the animal will exhibit anaphylactic specificity, as it can only be shocked by the original antigen or a closely related protein The lowering of the incubation time in an accelerated serum sickness reaction is a typical anamnestic response Finally just as it is possible to transfer passive immunity the anaphylactic sensitivity of an injected animal can be *passively transferred* to a normal one who can subsequently be shocked by administration of the antigen This passively conferred sensitivity will generally be retained for about two weeks This indicates that circulating in the blood are sensitizing antibodies as well as precipitins

Demonstration of the above mechanism in allergy is not as clear cut It is true nevertheless that except for contact and physical al

lergy the offending allergens are all specific protein substances or haptenic compounds. Furthermore, the allergic patient will show cross reactions with substances similar to the offending allergen which are of about the same grade of intensity as the cross reactions observed among these substances serologically. It is also possible to use allergens as normal or sensitizing allergens in animals, thereby demonstrating their antigenic properties. However, the way in which the allergic individual is initially sensitized is not always clear. It is in this phase that heredity plays such an important role. The antigens which the allergic patient responds to are substances which all individuals come in contact with regularly. In hypersensitive individuals a hereditary predisposition exists to respond to these relatively superficial contacts by the production of specific reagins. Although genetically a person may be susceptible to multiple sensitivities, these lie dormant until contact with the allergen has been made. The ways in which allergens may enter the body will be discussed later, but there is good evidence that foods can pass through the intestinal wall unchanged. Inhalants would sensitize by passing through or into the nasal mucosa. The importance of contact in pollinosis is dramatically illustrated by an experiment described later in this book, in which it is shown that despite a definite susceptibility, clinical symptoms of pollinosis do not appear until exposure to the offending agent.

Although allergic patients never show circulating precipitin antibody to their offending allergens (one possible exception to this is serum sickness), it is still possible to demonstrate circulating sensitizing antibodies or reagins in their blood. The best technique for showing this is the Prausnitz-Kustner reaction. Serum from an allergic individual is injected intradermally into a normal test subject. After twenty-four hours or more, the offending allergen is applied to the sensitized area of the normal individual and to a control area. A typical wheal will appear at the point where the allergic serum was introduced but nowhere else. It was formerly believed that reagins (the sensitizing antibodies of atopic individuals) could only be demonstrated by the Prausnitz-Kustner technique and this was presented as one of the major points of difference between atopy and anaphylaxis. However, it has recently been shown that although the reagin is normally present in the blood in very small amounts, it shows the general characteristics of any sensitizing antibody. Trans-

fusions of allergic blood have led to the development of temporary hypersensitivities in the recipients which mimic those of the donors Both cutaneous and shock tissue sensitivity has been obtained. Furthermore it has been possible to transfer antibodies from anaphylactically sensitized animals to normal human skin and obtain a positive skin reaction to the specific antigen Therefore the essential similarity between reagin and the sensitizing antibody found in anaphylaxis has been shown

Reagins are probably formed in the same sites as are other antibodies However it is possible to determine reagin concentrations in various parts of the body by direct application It has been shown that a greater concentration of reagin exists at those points where the antigen has been injected or otherwise brought into contact with the individual It therefore appears that the human at least can form antibodies in all his connective tissue elements

The simultaneous appearance of precipitins and sensitizing antibodies in anaphylaxis and serum sickness has brought up the question of whether these two substances are the same It must be borne in mind that antibodies formed after the administration of a specific antigen are not of a homogeneous character but differ in the ways discussed in the previous chapter Therefore depending upon what portion of the antigen the antibody was formed upon or how clearly it received the impression of its template an antibody may show the ability to react in the precipitin reaction or to sensitize the individual Some antibodies may possess both functions When hypersensitivity is created experimentally this dual phenomenon is always observed It is believed that desensitization involves this mechanism In hay fever administration of the offending pollen raises both the reaginic titer and the amount of allergen neutralizing antibody This is mentioned to point out again the essential similarity between atopy and anaphylactic sensitization since simultaneous precipitin and sensitizing antibody formation has been shown in the latter

Localization of the Hypersensitive Antibody Antigen Reaction on the Cell

Two theories have been proposed to account for the severe reactions ensuing when an antigen is injected into a sensitized individual One maintains that the reaction occurs in the blood liberating a

toxic product. However, the most acceptable theory is the one which postulates that reagin or sensitizing antibody becomes attached to specific cells and that subsequent administration of the antigen leads to the formation of an antigen-antibody complex on the surface of these cells

The evidence is as follows In the passive sensitization of an animal or human, a latent period must elapse before a hypersensitive reaction is obtained on administration of the antigen This should not be the case if antibody antigen combination occurred in the blood but would be expected if it were first necessary for the antibody to be distributed to the cells and become attached to them A peculiar reaction which has been observed is that of reverse passive transfer If a large dose of antigen is given a normal animal and shortly afterward a dose of sensitized serum, an anaphylactic reaction will occur as soon or sooner than in the normal type of passive sensitization This phenomenon is of importance in the transfusion of sensitized blood Another observation which indicates that the hypersensitive reaction occurs on the cell is the fact that when an animal is passively sensitized a marked lowering in the blood concentration of injected antibody occurs during the latent period Sensitizing antibody evidently leaves the circulation and becomes attached to the cells during this period

One of the most convincing pieces of evidence that the reaction is cellular is the fact that when certain tissues from a sensitive animal are isolated and washed thoroughly, addition of the specific antigen to the surrounding fluid causes a marked contraction of the tissue This can be observed in organs containing large amounts of smooth muscle This is so specific that sensitized guinea pig uterus is often used as a test for proteins Furthermore once the tissue has responded to administration of the antigen subsequent administration of this same protein has no effect The antigen evidently remains bound to the cell If the animal from which the tissue was obtained had de [illegible]

[illegible]

appearance of an anaphylactic reaction upon administration of the

antigen In fact the blood is more a protective medium than any thing else We have noted above the simultaneous production of precipitin with sensitizing antibodies in an anaphylactic or allergic organism *The precipitin or neutralizing antibody evidently has the* ability to combine with administered antigen and prevent its reaching the sensitized tissues This is believed to be one of the major reasons why it is so difficult to produce anaphylactic shock in the rabbit This animal produces a very high titer of precipitin when given a foreign protein Consequently upon subsequent administration of the antigen there is a great tendency for it to combine with the serum antibody and become neutralized Subcutaneous intraperitoneal and even intravenous injection of the antigen in a rabbit generally produces only mild symptoms It is necessary to inject the antigen intracardially to produce a consistent anaphylactic response In this way the antigen is quickly circulated to the tissues before any extensive neutralization in the blood stream can occur Even as sensitive an animal as the guinea pig often shows a fairly mild response upon subcutaneous or intraperitoneal injection However injection of an adequate dose of antigen intravenously always produces fatal shock Neutralization of antigen by its specific antibody can be shown by making a mixture of the two proteins and injecting them into an animal sensitive to the antigen No result is produced This is a good test method for determining the extent of antibody production

Another observation which suggests that the allergic reaction occurs in the tissues is the Arthus phenomenon This is produced by the injection of an antigen subcutaneously into the same site in an animal After a sufficient number of injections the site becomes indurated, and a necrosis sets in which may be quite extensive This phenomenon is believed due to a degeneration of the blood vessels in sensitized sites

Results of Antigen Antibody Combination

Injection of the antigen into a sensitive animal produces the hypersensitive reaction This occurs in the shock tissues In the human being these tissues comprise the nose eyes gastrointestinal tract and skin for the less severe manifestations the bronchioles pulmonary arteries and liver in the more serious cases All severe

ise in the less crucial tissues but of the bronchioles leading to asphyxia is probably the most common cause of death This resembles anaphylaxis in the guinea pig which has a very extensive smooth musculature in the bronchioles Another type of death which is believed to occur resembles that found in the shocked rabbit In this animal, the pulmonary arteries have a considerable smooth musculature and death is caused by their extreme contraction leading to right heart failure The dog shows a third type of anaphylactic response There is a massive hemorrhage into the liver, the organ swelling enormously in size An anatomic observation upon this animal which may help explain this finding is the fact that the dog has an abnormally high development of smooth muscle in its hepatic venules The constriction of these veins would cause blood stasis in the liver This effect is believed to occur in some cases of human anaphylaxis In summary, hypersensitive reactions produce the following effects (1) A constriction of smooth muscle, (2) increased glandular secretion, and (3) transudation of fluids into the tissue spaces

Several theories have been proposed to explain how the antibody-antigen combination on a cell surface can lead to these effects The theory which has the greatest number of supporters claims that the effect is mediated by the liberation of a chemical substance from the tissues which has the ability to produce all these results The discovery of histamine and the elaboration of its pharmacologic action revealed similarities between the action of this substance and the symptoms obtained in anaphylaxis which were so considerable that histamine was postulated as the effector substance Later work showed the presence of histamine in many tissues and investigators demonstrated a pronounced rise in the histamine content of the blood during anaphylactic shock Furthermore the disposition of an animal to develop anaphylactic sensitivity parallels its response to histamine injection The guinea pig is very sensitive to histamine and is shocked by this substance It develops anaphylaxis very easily The rat on the other hand is resistant to histamine and is very difficult to ... ies most affected in ... istamine injection ... prevent

anaphylaxis in a sensitive animal. These compounds also show an antagonistic effect toward histamine. If a segment of gut from a normal animal is put into the gastrointestinal tract of a sensitive animal, an initiated shock will cause this nonsensitized segment to contract. This suggests that a chemical causes the intestinal contraction since no reagins were present in the grafted segments. The wheal obtained upon the injection of an allergen into a sensitive indi-

to hypersensitive individuals can markedly reduce their response to offending allergens. It would seem that desensitization to histamine has produced a lessening of the allergic response.

However, there have been objections raised to the histamine theory. These are based mainly upon the fact that there is a variable response in the blood histamine level in shock. Frequently after an initial rise the blood histamine will decline to low levels even though the animal is still in a shocked state. Some animals, such as the horse, show virtually no increase in blood histamine at any time during anaphylactic shock. Furthermore, attempts to treat hypersensitivity through the injection or ingestion of histaminase, an enzyme which specifically destroys histamine, have been for the most part negative. Another objection is the fact that in anaphylaxis various tissues respond in a way which differs from the results obtained with the "in vitro" addition of histamine.

Theories have developed which have tried to explain these discrepancies. One postulates that instead of just histamine, a number of chemical agents, each specific for a definite organ, are liberated in anaphylactic shock. Another claims that antigen-antibody combination occurs on the smooth muscle cells of the smaller blood vessels leading to marked constriction and that this is the cause of the disturbances. This latter theory would explain quite adequately the lethal symptoms observed in anaphylaxis but does not account as satisfactorily for the increased glandular secretion and the wheals or urticaria. There is a possibility that all these mechanisms may function in the production of allergic symptoms or anaphylactic shock, but as yet insufficient evidence is available to allow a clear decision to be made.

Drug Allergy

The ingestion of or exposure to many drugs leads to allergic responses such as hives asthma or even severe shock like symptoms

monly found to cause hypersensitivity However these substances are not identical with the drugs themselves since they are made in such a form as to be tightly bound to the proteins with which they are injected Consequently many investigators have postulated that when a drug causes hypersensitivity it becomes altered in the body in such a way that it can form a fairly firm union with one of the body proteins leading to formation of a haptenic protein complex

tivity in the guinea pig upon continued application These substances and arsphenamine have also been used to produce anaphylactic sensitivity in the same animal and death could be caused by administration of the sensitizing compound Anaphylactic sensitivity has also been produced in the guinea pig by the injection of azo dyes Other drugs and natural products have been used to produce skin sensitivity in various animals

Allergic conditions caused by drugs will be discussed more fully in Chapter X

Gastrointestinal Allergy

Since the various ingestants which produce gastrointestinal and food allergy are all protein substances the mechanism by which they produce hypersensitivity is questioned The complex factor here is how these protein molecules are able to pass the intestinal wall intact and so cause the production of specific antibodies It was previously believed that no whole protein could pass through the intestinal membrane unless a very pathologic condition existed Nevertheless current immunologic studies have shown that this is not the case and

that even under
the food protein
develops a sensitivity to them depends upon his genetic composition

Some of the evidence which indicates the entrance of intact food molecules into the body may be cited Animals which have been fed large amounts of certain foods may sometimes demonstrate antibodies to these food proteins without being immunized If an individual who is hypersensitive to certain foods is given a transfusion of blood from an individual who has shortly before eaten some of the offending food, a very severe allergic response may be initiated Furthermore, Ratner has shown that if guinea pigs are fed cow's milk, a substance which is not normally in their diet, many become so sensitive to this substance that they can be anaphylactically shocked by it. In view of the passage of intact food protein into even the normal body it is probable that with a pathologic gastrointestinal tract the amount absorbed may be greater Consequently, a colitis or other intestinal upset in an infant who possesses a hereditary susceptibility to food allergy may initiate the hypersensitive syndrome.

Another way in which hypersensitivity can be developed is by
cally susceptible, the
the pregnant mother
he placenta, stimulate
reagin formation in the fetus If the mother herself is food sensitive, her reagins may pass the fetal barrier and passively immunize the fetus for a period of about six months after gestation

Similar considerations apply to the development of inhalant allergies Ratner has shown that guinea pigs can become anaphylactically sensitized to horse dander through the inhalation of large amounts of this substance The necessity for an initial exposure to the inhalant even in atopic individuals has been shown previously. It may be that intrauterine sensitization plays a role here also

Physical Allergy

Physical allergy is the response of certain individuals in a hyper-
Their typical
There can be
no question that an antibody antigen reaction is not involved here.

These individuals are generally sensitive to other types of allergy It may be that these cases initiate their hypersensitive reaction through a nervous mechanism but possess in their tissues an over developed ability to secrete the causative substance

Bacterial Allergy

to bacteria and bacterial
These allergies are often
he disease which caused
them There is a considerable degree of specificity in these reactions

man phenomenon This is similar to the Arthus reaction but more severe The site of injection of the bacterial protein in the hyper sensitive individual shows a very extensive and complete necrosis The reason for the difference in severity between the Arthus and the Schwartzman phenomena has been indicated in tissue culture experiments Addition of bacterial antigen to a tissue culture of cells obtained from an animal sensitive to the bacteria causes death of the cells Addition of antigen to the cells of an animal which has been sensitized to a protein other than a bacterial one has no effect upon the growth of the cells

Gastrointestinal physical and bacterial allergy are discussed in more detail in Chapter XI

Chapter IV

Seasonal Pollinosis or Seasonal Hay Fever

HISTORICAL

That hay fever is due to sensitization to pollens is not a new discovery A very accurate description of the symptoms was written by Bostock in England in 1819, in an article entitled *A Case of Periodical Affection of the Eyes and Chest*, published in the Medico-Chirurgical Transactions of London John Elliotson, another Englishman, was probably the first to record pollen as a probable cause of hay fever in 1836 In 1873, Blackley undertook very accurate experiments to identify the grass pollens as a cause of hay fever. He undoubtedly was the first to make use of cutaneous reactions

Among the earlier students of this problem in the United States, mention should be made of Worrill Wyman, who in 1876 wrote a monograph on *Autumnal Catarrh*, in which he accurately describes fall hay fever and ascribes its cause to the pollen of ragweed

William Daly of Pittsburgh in 1882 first called attention to hyperesthetic areas of the nasal mucosa in the hay fever victim

Sojour in 1883 presented his theory of hyperesthetic zones as responsible for hay fever Many other rhinologists confirmed these reports, each as a rule having found a slightly different hyperesthetic zone

Ingalls, in 1896, wrote that heredity and the neurotic diathesis undoubtedly predispose to this condition while a great variety of

agents may excite the attack Among these he mentions pollens but emphasizes that three essential factors are necessary the neurotic habit local hyperesthesia, and the presence of irritating substances in the atmosphere The treatment in vogue at that time was nasal cauterization

Dunbar in 1907 extracted a chemical substance from pollen which appeared to contain the active irritant He concluded that it was a toxin attached to albumin, and called it a toxalbumin Dunbar produced an antitoxin from horse serum which he called pollatin and used it locally in the eyes and nose, reporting excellent results in 56 per cent of cases Metzer and his pupils Auer and Lewis in 1910 brought this disease within the realm of the allergic diseases

In 1911, Freeman and Noon published results on the treatment of hay fever by active immunization with pollen extracts

Cooke in 1915 reported on 144 hay fever patients treated by injection with pollen extracts Since this time important pollen producing plants have been added to the list and methods of extracting the active principle of pollens have been more or less standardized

ETIOLOGY OF SEASONAL POLLINOSIS OR SEASONAL HAY FEVER

The causative agent of seasonal pollinosis is pollen, a light, yellowish, granular powder composed of particles which are microscopic in size and are produced in the reproductive cycle of the causative plant, whether it be a tree, grass, or weed It is rather obvious that this pollen must be light enough to be air borne in order that it may gain entrance through the respiratory tract

The production of pollen by plants is tremendous it having been estimated that many tons of pollen are deposited nationally in a given season Field surveys and pollen counts have been made for practically all areas in the United States

Characteristics of Pollen

Pollen granules consist chemically of a complex polysaccharide protein nucleus covered by a fatty layer The present-day consensus is that the acid secretions from the mucous glands in the nose eyes and respiratory epithelium disintegrate the fatty covering of

the pollen granule and thus make available the soluble protein and polysaccharide fractions

It has been estimated that pollen can be found in the atmosphere at a height of 10 000 feet and that it may be carried over a body of water for many miles Pollen can be blown into an area from a distance as great as 600 miles as is shown by the invasion of Canadian thistle into this country in the past few years

The amount of pollen in the air depends upon meteorologic fluctuations The greatest amount of pollen is present in the surface air layers toward evening and in the early morning It is during these periods that hay fever patients sneeze most This is mainly the result of two factors an increased circulation of the air due to the temperature changes caused by the rising and setting of the sun, and second, the increased general humidity which exists at these times close to the earth s surface (dew and fog formation) The increased atmos pheric circulation brings down pollen from the higher air layers which is trapped, together with the pollen originally present, by the moisture in the air A high humidity no doubt traps pollen by using the grains as points on which condensation can occur The buoyancy of the wet grains would be materially decreased and the over all effect would be a marked increase in the concentration of pollen directly over the surface of the land Later in the day or evening, when the circulation of the air slows and the humidity returns to normal, the pollen again redistributes itself evenly On rainy days the air is washed of pollen and patients ordinarily are considerably relieved, while on sunny days the plant pollen is quickly dried and released from the plant Strong winds tend to disperse the pollen over large areas A region close to a body of water will have less pollen in the air on days when the wind blows from the direction of the water Inasmuch as the patient's symptoms vary directly with the quantity of pollen present in the air these factors are clinically important in correlating and understanding the day by day progress and course of the patient

A list of hay fever plants and their locations will be found in the Appendix

Our Technic of Pollen Counts At best pollen counts cannot in dicate the exact concentration of pollen grains despite attempts that have been made by Durham and others to accurately determine the

amount of pollen and mold spores in the air at various localities Various complicated conversion tables have been worked out by Durham for each pollen and several mechanical devices are on the market for obtaining the pollen on glass slides by the gravity method These however are too complicated for ordinary use Pollen counts are only important when made in the vicinity of the patient The pollen grains can be identified and then the proper extract can be given in treatment

One of my patients obtained very slight relief under treatment with a 50 per cent giant and short ragweed mixture which was the most prevalent pollen in that city s atmospheric count He owned a large coal and lumber yard and it was found that he was surrounded with fields of heavy growth of cocklebur Complete relief of symptoms followed a year s treatment with cocklebur pollen extract Durham states that cocklebur pollen is not important because atmospheric counts show only small amounts in the air While the pollen from the plant may not be found on slides taken perhaps many miles from the patient s vicinity the more important procedure is to expose slides close to the patient s environment In this way a more exact study can be made of the pollens to which exposure occurs constantly I have found this procedure of greater importance and far more valuable than the daily counts of pollen as reported by various observers

I use a simple device consisting of a wooden base to which is attached a monel metal rustless top in the shape of a convex curve with openings on both sides Microscopic slides covered with a thin layer of vaseline are placed on the base and allowed to remain for twenty four hours The top prevents rain and soot particles from contaminating the slide while allowing air currents to impinge pollen and mold spores on the greased slide

The actual count is made under the low power of the microscope counting all pollen grains covering one square centimeter on the slide This is the figure approved by the pollen survey committee of the American Academy of Allergy The amount of pollen grains *counted in 1 square centimeter of slide area multiplied by 3 6* will give the approximate number of pollen grains per cubic yard of air The figure 3 6 has been determined and adopted for universal use by the Committee of the American Academy of Allergy It should

be remembered that pollen concentration in the air varies in accordance with changing meteorologic fluctuations such as wind velocity, changing directions of winds, fog, dew, and rain.

CLINICAL SYMPTOMS

The name hay fever suggests that the symptoms are caused by hay and that there is an actual fever present. However, the symptoms are not due to hay, and there is usually a subnormal temperature.

In hay fever *there is an inflammation of the mucous membranes* of the nose, throat, ears, eyes, and, sometimes, of the bronchi and bronchioles. This inflammation manifests itself clinically as sneezing, running and blocking of the nose, and itching of the eyes, nose, ears, and throat. The difficulty in nasal breathing usually present is aggravated when the patient is lying down and seems to be lessened when he is exercising. Characteristically, the nasal discharge usually remains thin and watery and becomes thickened only toward the termination of the attack. After the nasal congestion and swelling of the turbinates and mucosa of the nose have been present for some time, the tissues become a favorable cultural media for bacterial organisms, and a thickening of the secretions with purulent discharge follows. This sequence of events frequently results in chronic sinus infections which many times so obscure the picture that the primary allergic background is not recognized. While the eosinophils are increased in the watery nasal secretion at an early stage in hay fever, they almost disappear and are replaced by polymorphonuclear leukocytes when bacterial infection occurs.

Hay fever symptoms, if they persist, will usually terminate in cough, dyspnea, and wheezing, leading to the development of a full-blown bronchial asthma.

Also characteristic of hay fever is marked malaise and easy fatigability, together with a sensation of fever in the presence of a subnormal temperature. *These complaints are due to absorption of the* allergenic protein, causing "allergic toxemia."

DIAGNOSIS

The diagnosis of hay fever rests upon the history, the physical examination, the laboratory examination, *and the therapeutic response.*

One of the most important steps in arriving at a diagnosis of seasonal pollinosis is an accurate history, containing the dates and places of onset of the initial symptoms One should always inquire for dates which may furnish valuable clues as to the type of pollen responsible, for example, if a patient reported initial symptoms near Decoration Day, one would suspect tree pollens as the etiologic agent, symptoms appearing around the Fourth of July would make grasses the likely cause, while an onset on Labor Day would implicate the ragweed group One should also inquire as to whether the patient has done any traveling and what symptoms, if any, appeared or disappeared during this journey A patient may, for example, tell the doctor that he spent his vacation in Indianapolis around Labor Day, and that his condition was much worse at that time The doctor will then have good reason to suspect a ragweed pollinosis since Indianapolis is known to have a high concentration of ragweed pollen during September (see the Appendix for a list of pollen locations in the United States) The patient may have noticed his first symptoms while in the country and this would lead the physician to suspect a pollinosis since the pollen concentration in the country is higher than in the city

The family history and the past history must be obtained A previous allergic manifestation on the part of the patient, such as eczema, hives asthma, or food sensitivity, may be disclosed and the existence of allergic disease in the patient s family may be revealed

Another important line of inquiry is that devoted to eliciting the organs and tissues involved and the physical examination of the hay fever patient should be a complete one, with particular attention being paid to the examination of the conjunctivae of the eyes, the nasal mucosa and turbinates, pharynx and chest One must look for injection of the conjunctivae and the fine linear conjunctival scars resulting from repeated contact with pollen from previous years In the nose, the inferior turbinates and nasal mucosa have a grayish white, waterlogged boggy appearance and the posterior portion of the inferior turbinates may be hypertrophied The pharynx may present a mild injection An examination of the chest will often reveal diffuse wheezing and moist râles over the larger bronchi Minimal asthma may be detected in many cases only by placing the diaphragm of the stethoscope over the open mouth of the patient

as he breathes By this method, one may often detect fine musical râles not heard by ordinary auscultation

The laboratory examination should include the usual blood and urine studies, nasal and ocular smears for eosinophiles, and skin testing The latter is the most important part of the laboratory investigation.

Testing Technics

The skin, eyes, and nose will respond in a characteristic way to application of the allergen All of these may be used in testing the patient to find offending substances The skin test is the safest and most convenient and is sensitive enough to be adequate in over 99 per cent of the patients

Cutaneous or Scratch Tests In the cutaneous or scratch test the skin is thoroughly cleansed with alcohol, after which small linear, bloodless scratches in the epidermis are made with an ordinary darning needle or a dulled von Graefe knife The smallest possible scratch is sufficient to elicit the full response of the skin The scratches are made about ⅛ inch long, and 1 inch apart on the arms, forearms, back, or thighs As many as 50 can be made at one sitting A small drop of a 3 per cent solution of the pollen extract is applied over each scratch mark and rubbed in with the sharp end of a tooth pick (a separate toothpick is used for each application) After twenty minutes these extracts are wiped off with water and the reactions read Each scratch mark should be cleansed individually with care taken to prevent contamination of adjacent scratch tests

A positive reaction to such a skin test is essentially the same as a hive or a mosquito bite a central whitish or yellowish swollen area surrounded by a reddish zone or areola The central area may be round in outline or may extend outward in irregularly shaped branchings or pseudopodia of varying lengths, somewhat resembling an amoeba These reactions are generally accompanied by itching

There is considerable variation in response to these tests in highly sensitive patients the swollen area may be very large and red, whereas other individuals show only slight redness and itching Regardless of whether the reaction is intense or mild its peak is reached in about twenty minutes and it subsides after an hour This method of testing

has the advantage of giving rise to a minimum of constitutional reactions and is therefore safer in the hands of the general prac titioner

INTRADERMAL SKIN TESTS

In this technic a small amount usually 0 01 cc of a specially prepared liquid extract of the suspected substance is injected between the layers of the skin No exact quantity is used in practice but one should inject an amount sufficient to raise a small bleb in the epidermis larger amounts should not be injected because of the ever present danger of constitutional and false positive reactions A tuberculin syringe and a 27 gauge 3/8 inch rustless needle are sterilized by boiling and used for this purpose The outer arms outer surface of the thighs and the back are the best sites for these tests The skin is cleansed with 70 per cent alcohol and the injections given from above downwards usually ten to fifteen in each arm spaced about one inch apart

This method is cleaner less painful more rapid and more sensi tive than the scratch test but it yields a greater percentage of false positive reactions and occasionally gives rise to a serious constitu tional reaction It is of the greatest value in testing hay fever asthma and allergic dermatoses but is of no value in testing contact der matitis and drug allergy

The appearance of a wheal especially with pseudopodia and a surrounding area of erythema indicates a positive reaction This reaction is read as slight moderate or marked depending upon the size of the wheal and the number of pseudopodia Occasionally the reaction may be doubtful or slight but on waiting twenty four hours a definite positive reaction may occur which then is called a delayed reaction False positive reactions occur frequently in a highly sensi tive skin while refractory or atrophic skin will fail to give a positive reaction even when clinical sensitivity exists Furthermore the re action depends upon the concentration of the extract employed in testing

In testing a pollen hay fever patient the most dilute extract which will give a reaction in a sensitive individual is used This dilution may vary from a 1 10 000 to a 1 1000 concentration The exceptional

patient may be so sensitive that it may be necessary to start with a 1 100 000 to 1 1000 dilution of pollen extract

Intradermal skin testing is not a static technic The allergic individual is likely to develop new sensitivities at any time situations arise where one year the skin tests show a positive ragweed reaction and a negative grass whereas the next year the tests will show a positive grass and a tree reaction This characteristic of the allergic patient necessitates repeated and frequent skin testing

It will often be noted in practice that a ragweed sensitive patient may show a positive grass and tree reaction yet have no symptoms during the pollination of these plants However the following year symptoms may occur during the tree and grass seasons These patients are potentially allergic to grasses and trees and can develop symptoms at some future time if not hyposensitized

Conjunctival Testing This test is performed only when there is strong clinical evidence of pollen allergy in a patient whose intra dermal skin test is negative or doubtful This procedure should not be carried out routinely because of the possibility of a severe local reaction involving the entire conjunctivae of the eye

It is performed by placing a drop of the dilute extract or a few grains of the dry pollen in the conjunctival sac If within a few minutes the conjunctival vessels are markedly congested and the eye is red with lacrimation and itching the test is positive The physician should immediately instill a drop or two of a 1 1000 epinephrine solution into the conjunctival sac to counteract the local reaction

Nasal Test or Sniff Test This test is rarely used in the diagnosis of pollinosis A few grains of the pollen or a few drops of the pollen extract are instilled into the nose The test is positive when marked sneezing and a watery discharge from the nose ensue

Passive Transfer Test (Indirect Test or Prausnitz Kustner Phenomenon) This test is useful in cases where it is impossible to do direct testing on the patient as in patients whose skin is extensively involved in a severe dermatitis or who are highly dermographic It may also be used when the above methods have all given negative results but where clinical evidence still indicates that a pollinosis exists

The skin of a normal person is sensitized by the injection of 0 1 cc of serum from the patient Forty eight hours after injection of the

patient s serum into the normal skin one may skin test (intradermal or scratch) the sites into which the suspected serum was introduced A control should always be run by skin testing with normal saline into one of these areas The appearance of a wheal indicates a sensitivity of the patient to that pollen or substance

DIFFERENTIAL DIAGNOSIS

The disease most difficult to differentiate from hay fever is acute coryza or common cold during the first twenty four hours Usually the coryza is characterized by more malaise slight fever headache less itching of the nose and eyes and more rapid progression to the state of a thickened purulent nasal secretion In pollinosis the sneezing is most marked in the morning and decreases in severity towards afternoon in coryza there is a steady progression of symptoms with continuous sneezing and a watery discharge leading without interruption into the phase of thickened nasal secretion Nevertheless in the first twenty four hours of an acute coryza the differential diagnosis from pollinosis will tax even the most astute clinician Nasal smears may help if they reveal eosinophils but are not completely reliable

SINUSITIS

Sinusitis may accompany any inflammation of the nasal mucosa regardless of etiology however it is important to distinguish between bacterial inflammation with sinusitis and pollinosis remembering always that pollinosis predisposes to the development of a bacterial sinusitis The onset of sinusitis is more acute and is characterized by a purulent nasal secretion intense headache and localized tenderness over the paranasal sinuses accompanied by fever X ray of the sinuses will usually reveal some cloudiness Intranasal examination will show swollen red membranes with evidence of pus draining from one of the orifices of the turbinates

DEVIATED NASAL SEPTUM

A deviated nasal septum of severe degree may cause sneezing and rhinorrhea which will resemble hay fever but other evidences of pollinosis are not apparent and physical examination confirms the diagnosis

Nasal Polyps

Nasal polyps are a likely sequelae to a long standing untreated pollinosis or other inhalant allergy and are diagnosed by inspection The polyps are usually seen as pale, whitish gray swellings which can be visualized in the middle or superior meatus of the turbinates

Mechanical Irritants

Mechanical irritants such as high concentrations of dust, sand, silica, and foreign matter of all types will produce sneezing with a purulent rhinitis which may at first sight be mistaken for an allergic condition The history will establish the diagnosis

SYMPTOMATIC TREATMENT OF POLLINOSIS

When the patient presents himself with symptoms of pollinosis, the following local measures may be used If no history of relevant drug sensitivity is obtained one of the various antihistaminic drugs (see page 46) should be used in doses of 25 mg or 50 mg every three to four hours It is best to begin with the smaller dose and decrease the intervals between doses until relief from symptoms is obtained When side reactions occur, the drug should be stopped entirely until these symptoms disappear Several of the antihistaminic drugs may have to be tried until one is found which does not seriously affect the patient

For the eye symptoms, the following drops used in the eyes every two to three hours will alleviate the itching and relieve the inflammation

Epinephrine hydrochloride 1 1000	0 6 cc.
Dilute acetic acid	0 2 cc.
Resorcin	60 0 mg
Distilled water, to make	30 gm

Many patients get adequate relief of their ophthalmic symptoms from the use of the simple eye cup with dilute boric acid solution, or a solution of oxycyanide of mercury 1 5000 Antistine 0 5 per cent solution has a pH of 6 94 and two to three drops instilled in the eye every three to four hours is quite helpful Some patients complain of an initial burning or stinging sensation which may last for a few

minutes It should not be used too frequently or over too prolonged a period of time since I have seen a sensitivity develop to this drug after prolonged use A marked membranous conjunctivitis with intense itching resulted in one of my patients who used antistine locally in the eyes for an allergic conjunctivitis Neosynephrin, ⅛ per cent solution, is also useful in the eyes

For excessive nasal symptoms, privine hydrochloride 05 per cent gives adequate relief when used as a spray, jell or drops instilled into the nose every six hours Too frequent use, however, may result in an increase of the symptoms due to increased congestion which follows the vasoconstrictor effect

A 0 5 or 1 per cent ephedrine solution in normal saline solution will also relieve the nasal congestion Oily solutions are not used as they are too irritating to the sensitive nasal mucosa and because of the danger of oil aspiration with subsequent development of lipoid pneumonia Fabricant has demonstrated that the normal pH of the nasal secretion is on the acid side and nasal medication with a pH on the alkaline side (above 7 4) acts as an irritant to the sensitive mucosa, interferes with the normal ciliary activity, and thus increases the symptoms It is for this reason that ephedrine and other vasoconstrictors in water, all of which give highly alkaline reactions, increase nasal symptoms whereas medications such as privine, propadrine hydrochloride, ephedrine in normal salt solution neosynephrin 0 25, 0 5, or 1 per cent solution paredrine 0 5 to 1 per cent glucophedrine, tuamine, isohalant, and vonedrine are more soothing because of their more acid reaction having a pH of 5 5 to 6 5 Inhalers of benzedrine, tuamine, forthane or vonedrine often give relief where drops are not desirable

Many of the antihistaminic drugs are also used locally in the nose such as pyribenzamine 0 5 per cent solution and antistine 0 5 per cent solution I have found them to be quite irritating on sensitive mucosa causing burning with increased sneezing

The use of calcium, iodides morphine cocaine, codein, and vitamin C for the relief of pollinosis is mentioned only to condemn their use They are of no value in pollinosis and may even increase the nasal symptoms

General measures such as avoidance of dust, swimming, exposure to the sun heat, fatigue, golf, and automobile rides through the

country are advised The diet should be carefully watched and all foods that the patient is found sensitive to, either by history or skin tests, eliminated All environmental factors such as orris root, feathers, molds, dust, pyrethrum, and other animal emanations should be carefully checked and avoided should they be found to be additional sensitizing substances

Nasal ionization is of no benefit in pollinosis The same effect may be obtained with any escharotic agent such as 95 per cent phenol, strong silver nitrate, or the use of the cautery Local treatment of any type including nasal packs adds additional irritation to an already inflamed, sensitive membrane with resulting sneezing and increased congestion Following ionization for pollinosis, anosmia and neuritis of the nasal ganglia with severe pain may follow Also, hyperesthesia of the sense of smell has resulted following its use

Pollinosis must be considered a constitutional disease with local manifestations and should be treated as such Any severe local or operative nasal treatment to an already highly sensitive nasal mucosa does more harm than good The removal of tonsils and adenoids is certainly not indicated as a relief measure in pollinosis In any case they should not be removed during the pollen season Highly allergic children in particular should not have the tonsils and adenoids removed without a definite indication In a large series of cases collected over a long period of time the removal of tonsils and adenoids in children of allergic families has been shown to result in the onset of pollinosis or asthma Should a definite indication exist, such as repeated tonsilar or adenoid infection, greatly hypertrophied tonsilar and adenoid tissue, or repeated otitis media resulting from infected adenoid tissue it is better to have them removed—but certainly not during any pollen season The removal of these tissues because of repeated colds is not indicated

Antihistamine Therapy

Dale and Laidlaw, in 1910, noted the resemblance between histamine shock and anaphylactic shock in guinea pigs Lewis, in 1927, stated that a histamine-like substance, which he designated as H substance, was liberated by the tissue of humans at the site of the allergic reaction Dragstedt added evidence of the importance of

histamine in human allergy, and made the following observations

1 Similarity between anaphylaxis in animals and allergy in humans

2 Evidence of the presence of histamine in human tissue in sufficient quantity to produce symptoms

3 Similarity between allergic symptoms and histamine effects Severe allergic symptoms actually resemble the effects produced by large doses of injected histamine

4 Histamine or a histamine substance is actually released from the cells during allergic reactions in humans

Katz and Cohen demonstrated that histamine is released from the cells to the plasma when an antigen is added to the blood of an allergic patient Katz showed, further, that histamine is released from the skin when an antigen is applied to the skin of an allergic patient The good results from antihistamine therapy in allergic conditions, particularly of the true atopic wheal reactions such as urticaria, hay fever, serum and pollen reactions, and physical allergy, add additional evidence that histamine or H substance plays some definite role in these conditions

Many investigators, however, are of the opinion that there are other factors beside histamine responsible for allergic or anaphylactic symptoms They point to the failure of the drugs to relieve asthma and other types of allergic disorders The direct, positive identification of histamine in human blood has so far not been made Actually it has been shown by Watanobe that histamine is stored in the lungs of guinea pigs and the liver of dogs following sensitization, and that during anaphylactic shock histamine is released, the amount stored in these organs dropping sharply

Code and Hester observed a fall in the blood histamine of the calf and the horse during anaphylaxis, while Rose noted a similar occurrence in the rabbit These facts are in direct opposition to the full acceptance of the histamine theory, although once again it should be pointed out that humans react in quite a different way from laboratory animals

Attempts to desensitize humans to histamine thus far have failed Histamine injections do not raise the tolerance to this substance nor reduce its manifestations

Hapamine Fill, Rodney, and Marshall coupled histamine to

various proteins by azo linkage to produce the so-called histamine azo protein They thought this product called hapamine would desensitize the body to histamine However, it has been a total failure in my experience and the experience of others The Committee on Therapeutics of the American Academy of Allergy concluded after an extensive clinical trial that hapamine was totally ineffective Whatever effectiveness it had can be attributed to its nonspecific action

Histaminase Best in 1929 demonstrated that some tissues contain an enzyme capable of destroying histamine when the two are mixed and incubated in a test tube This substance was marketed under the name of Torantil and soon after its clinical use conflicting reports appeared in the literature The Council on Pharmacy and Chemistry of the American Medical Association reported on histamine and Torantil in 1930 stating that there was insufficient evidence of clinical value and omitted its inclusion in new and nonofficial remedies

Best and McHenry in 1930 likewise stated that the intravenous or intramuscular administration of histaminase has no effect upon histamine present in the body or after injection This has been my experience and also the experience of most allergists

Other Histamine Antagonists Since Lewis suggestion in 1927 (see above) attempts have been made to find some nonspecific substance which would inhibit any allergic and anaphylactic reaction, regardless of what the antigen might be

Certain groups of amino acids such as histidine arginine and cysteine were demonstrated by Edebacher Tucker and Baur to have inhibiting actions on histamine in laboratory experiments However they were found too toxic for use in humans and animals Landau and Gray in 1944 demonstrated that monohydrochlorides of arginine and histidine prevented the effect of histamine or an antigen on a strip of guinea pig intestine They concluded that these substances were too toxic for clinical use

Fourneau and Bovet reported in 1933 on the use of a phenolic ether compound having the property of inhibiting the action of histamine They named this compound 929 F with the chemical formula 2 isopropyl 5 methyl phenoxyethyldiethylamine Staub and Bovet found that compound 929 F had definite antianaphylactic

properties since it protected guinea pigs against two lethal doses of histamine However it also produced toxic effects in animals and could not be used clinically in humans

Compound 1571 F a Fourneau product containing the ethylendi amine radical having the following formula N phenyl N ethyl N diethyl ethylendiamine was the next product investigated by Staub who reported its antianaphylactic and antihistaminic activity This product was likewise found too toxic for clinical use

Halpern studied the effects of two compounds in 1942 prepared by Mosnier of France One of these antergan with the chemical formula N phenyl N benzyl N dimethyl ethylendiamine was found to be more effective as an antihistamine drug than all the previous drugs used Later neo antergan having the structural formula N p methoxybenzyl N dimetho amino ethyl a aminopyridine was found more effective and less toxic than antergan Halpern thought that neo antergan was a more useful drug because it was better tolerated This drug is the principal antihistaminic used at present in France

Benadryl hydrochloride or diphenhydramine hydrochloride was the first effective antihistaminic drug to be used clinically in America Loew Kaiser and Moore synthesized this drug in 1945 and useful results were reported in urticaria serum sickness angioneurotic edema and hay fever Its use has been rather disappointing in asthma and atopic dermatitis

The most common side reactions are drowsiness lassitude dizziness and mental incoordination These effects may be due to a depression of the higher brain centers On discontinuance of the drug these symptoms disappear

The drug is used in 25 mg and 50 mg capsules by mouth and in solution for intramuscular or intravenous injection One cubic centimeter of the solution contains 10 mg of benadryl With the use of smaller doses such as 25 mg three or four times a day the depressive side reactions can be averted

Tripelennamine hydrochloride (pyribenzamine hydrochloride) was the second American histamine antagonist produced in 1946 The chemical formula is N N dimethyl N benzyl N (alpha pyridyl) ethelendiamine monohydrochloride It differs from neo antergan only by the removal of the methoxy group from the benzine ring

Pyribenzamine and neo antergan are the most potent in inhibiting whealing effects in humans by urticariogenic agents

The most frequent side reactions are drowsiness, fatigue, gastro intestinal upsets, dizziness, nervousness, and dryness of the mouth Some patients seem to tolerate this drug better than benadryl

The antihistaminic drugs, according to an article by Robert E Miller, Robert G Taub, and the author and published in June, 1949 may be classified chemically into at least three empirical groups Although these groups are not strict in their chemical arrangement, they vary in most instances only in the placement of various side radicals

The *ether series* consists of benadryl and linadryl, and the *ethelen diamine series* of pyribenzamine, antergan, neo antergan, thenylene (histadyl) *neohetramine, decapryn, trimeton,* diatrin, hydryllin, pyrrhazalate, perazil, phenergan, and others Thephorin (Roche) (phenindamine) 2 methyl 9 phenyl 2,3,4 0 tetrahydro 1 pyridindene hydrogen tartrate, is a *pyridyl* base and thus differs from the other two groups above There is very little sedation effect produced, and stages of excitation may follow its use Insomnia and nervousness have been caused by its use

On this basis of classification many constitutional reactions may be predicted The ether series is more prone to act as a depressant of the nervous system, heart, and blood vessels Complaints of drowsiness, confusion, narcolepsy, and weakness and findings of dilated pupils are more prevalent with the ether series, while gastrointestinal complaints are more often encountered in the use of the ethylene diamine series Both produce marked weakness after prolonged administration This weakness continues even with the substitution of one series with the other, or with different members of the same group

Because these constitutional reactions are so often found and since the well defined pharmacologic reactions and organic effects of the antihistamines of all three groups are not completely known further extensive investigation should be made along these lines Quite like the unknown nature of the production of the allergic state in man the method by which the so called antihistaminic drugs act is not well defined

These facts make the inadequacy of this group of pharmaceuticals in relieving certain allergic conditions such as asthma migraine and atopic dermatitis understandable The immunochemistry of the antigen antibody reaction and its end products remains in a partially confused state It is well known that allergic manifestations change from day to day and year to year This plus the lack of knowledge of the action of the so called antihistaminics makes their evaluation most difficult

Their use has proven to be a good palliative measure although they have not given even partial gratification in manifestations other than in allergic rhinitis (perennial and seasonal) urticaria serum sickness and angioneurotic edema

Their action in my experience has been shown to be comparatively short lived and has in no instance afforded permanent arrest of the allergic symptoms These substances should be considered in their proper therapeutic place that of symptomatic relief and discontinued as soon as hyposensitization or elimination or both can be effected It should be emphasized that the antihistaminic drugs are useful as palliative measures during the period of determining the antigen or antigens responsible for the allergic state Since the exact mechanism of the antibody antigen reaction is at present a controversial issue and the role of histamine or a histamine like substance has not been definitely established etiologically it is felt that indications for the use of these drugs are limited

TREATMENT OF SEASONAL POLLINOSIS

The specific treatment of pollinosis consists of hyposensitization which term implies raising the patient s tolerance to the offending pollen Hyposensitization (introduced by Cooke) is used today rather than desensitization since it is highly doubtful whether we can ever render a patient completely insensitive to the allergen

Although hyposensitization has been clinically used for approximately thirty five years with considerable success until recently there was nothing known about the mechanism of this treatment It had been noted that although patients exhibited good clinical relief from hyposensitization treatments their skin reactions to the offending pollen were much more violent in areas which had not

been used as the injection sites, and a more pronounced reaction was observed in passive transfer experiments.

Recently, Loveless has done some important work on the more intimate details of this process. She has shown that continuous injection of the allergen does not cause a lowering of the atopic reagin content of the body. Rather, there is a marked increase in the quantity both of reagin and of circulating "thermostable neutralizing antibody." This latter substance, which is believed similar to a precipitin antibody, is conceived by her to be the substance responsible for neutralizing the effect of airborne pollens. She believes the process occurring in hyposensitization to be as follows: Injection of the offending allergen causes an accelerated production of both the reaginic antibody and of a circulating precipitin antibody specific for the administered pollen. Although the increased amount of reagin would tend to cause greater sensitivity on the part of the patient, the neutralizing antibody produced so overbalances in amount the excess reagin that an immunity to the offending pollen is produced Failure on the part of the allergic individual to produce a considerable excess of neutralizing antibody over reagin would lead to poor hyposensitization. This neutralizing antibody can be demonstrated by heating serum from a hyposensitized patient for one hour at 60° C. Mixing this serum with a dilute extract of the offending pollen and injecting the mixture into the skin of a sensitive individual will produce very little or no skin reaction.

There is some controversy over the relation of the relief of symptoms of hay fever and the amount of blocking antibody present. Loveless states that the higher the antibody titer, the greater the clinical improvement in a large majority of patients. Gelfand and Frank, however, maintain that clinical results do not depend upon high titers of blocking antibodies. They find that the percentage of good results is identical in those who had low and in those who had high titers.

The measurement of titers of blocking antibody by passive transfer neutralization does not produce consistent results. There is likewise no common standard in use today to estimate accurately degrees of clinical improvement of hay fever patients. There is a method of estimating the quantitative precipitin measurement of

thermostable antibody This entire question should therefore remain open until more work is done on larger series of patients along these lines

Comparison of Various Pollen Units

One of the important factors in the standardization of hyposensitization treatment is the adoption of a satisfactory method of measuring the strength of pollen extracts Unfortunately no standard unit has as yet been accepted universally

Pollen Unit of Noon Noon of England was the first to suggest a pollen unit He designates it as the quantity of allergen in an extract of one millionth gram of pollen One gram of dried pollen contains one million pollen units Therefore if 1 Gm of pollen is extracted in 100 cc of extracting fluid to make a 1 per cent solution (weight by volume) the entire 100 cc of extract contains 1 million units One cc will contain 10 000 units and 01 cc will contain 100 units If 1 100 pollen extract is diluted 100 times 01 cc of this solution will be equivalent to 1 Noon unit Dosages can be easily figured in units and will result in more uniformity when statistics from various allergists are compared

Weight by Volume, or Percentage Method For original extraction of pollen it is customary to make original strong solutions of 2 per cent or 3 per cent and from these stock extracts make further serial dilutions in multiples of ten Thus a 3 per cent or 1 33 solution is diluted with extracting fluid by adding 1 cc of the stock solution to 2 cc of extracting fluid resulting in 3 cc of a 1 100 solution By adding 1 cc of this extract to 9 cc of diluting fluid a 1 1000 extract solution results and 1 cc of the 1 1000 extract added to 9 cc of diluting fluid makes a 1 10 000 extract and so on

The Total Nitrogen Unit Cooke in 1915 proposed to standardize pollen extract by the determination of total nitrogen as an index of the protein content This was found to be inaccurate since not one but two or more proteins have been found in pollen

Protein nitrogen was suggested by Cooke and Stull as a more accurate measure of the protein unit They designate a protein unit as 0 00001 mg of protein nitrogen One hundred units would be 0 001 mg and 10 000 units are contained in 0 1 mg The concentration of an extract is thus expressed in units per cc The average

ragweed extract of 3 Gm per 100 cc of solution or a 1 33 would represent 16,000 units or 0 16 mg per cc A 3 per cent grass extract represents an average of 0 2 mg per cc

The following table shows the unit values of pollen extracts by comparison

	Dosage	Pollen units	*Total protein nitrogen* Milligrams	Units
Dilutions	1 cc 1 1,000,000	1	0 000016	0.64
(weight of	1 cc 1 100,000	10	0 00016	6.4
pollen per	1 cc. 1 10,000	100	0 0016	64 0
volume of	1 cc. 1 1000	1,000	0 016	640.0
extractive)	1 cc. 1 100	10,000	0 16	6400 0

It is known that pollen solutions lose their potency with age, *particularly if not refrigerated Sometimes this loss of potency will* reach 50 per cent The active ingredient in the pollen solution has as yet not been determined Stull (in 1942) found three protein fractions in pollen, of which fraction one seemed to be the most active in skin tests Rockwell found the antigen to be a polypeptide of high molecular weight containing large amounts of amino acids Black reports finding a polysaccharide which gave positive skin tests

Thus we see that there is as yet no uniformity regarding the nature of the antigenic substance in pollen Therefore the weight by volume method of standardization of pollen is the simplest and best method at this time

Technic of Hyposensitization

the same pollen in the same arm every time since this involves a local tissue hyposensitization which is quite high and local reactions are less severe

Treatment is usually begun with an injection of approximately 0 05 to 0 1 cc of the highest dilution that provokes a positive intra dermal reaction This dilution may vary from 1 10 000 to 1 50 000 and in extremely sensitive patients will be as high as 1 1,000,000 The injections are given at five to seven day intervals and the size of

the dose is never increased if a large local reaction manifests itself as edema and erythema with itching at the site, or if systemic reactions such as generalized urticaria pruritus hay fever, or asthma occur The appearance of these signs necessitates a repetition of the dose which produced the symptoms instead of an increase at the next injection In some patients it may even be necessary to decrease the amount given

The treatment is given as an ordinary subcutaneous injection with the usual sterile precautions and always with care being taken not to introduce any of the antigen intravenously The same type of tuberculin syringe used for testing is advisable for therapy because of the greater accuracy obtained in measuring the dose The extensor aspects of the upper right and left arms are used for the injections The dosage is increased according to the following schedule which has been found most useful in that the volume of the individual doses is small It must be realized that this schedule is very flexible and may be modified for each patient

Concentration		Concentration		Concentration		Concentration	
1:10,000		1:1000		1:100		3% or 1:33	
Dose 1	0.1 cc.	Dose 6	0.1 cc.	Dose 11	0.1 cc.	Dose 16	0.05 cc
Dose 2	0.2 cc	Dose 7	0.2 cc.	Dose 12	0.2 cc.	Dose 17	0.1 cc.
Dose 3	0.3 cc	Dose 8	0.3 cc	Dose 13	0.3 cc	Dose 18	0.15 cc.
Dose 4	0.4 cc	Dose 9	0.4 cc.	Dose 14	0.4 cc.	Dose 19	0.2 cc.
Dose 5	0.5 cc	Dose 10	0.5 cc	Dose 15	0.5 cc	Dose 20	0.25 cc
						Dose 21	0.3 cc
						Dose 22	0.35 cc.
						Dose 23	0.4 cc.
						Dose 24	0.45 cc
						Dose 25	0.5 cc.

The peak dose is the highest dose which the individual patient will tolerate without producing constitutional symptoms or severe local reactions There is no fixed rule as to what this dose is and it is best determined by the physician who is treating the patient how ever it is not necessary to increase the dose beyond that which gives the patient the optimum of relief

In a survey of top pollen dosages used by various allergists through out the United States I note quite a variance The men in the East use much smaller top doses than those in the Midwest and West The reason for this is quite clear since the pollen counts in the East are far lower than those in the Midwest and West (see Pollen Records

for 1939 in the Appendix) Also the ragweed season is *shorter* in parts of the East compared to that of the Midwest The top pollen dose in this vicinity ranges from 20 000 to 30 000 units or 1 cc of a 2 per cent (1 50) solution to 1 cc of a 3 per cent (1 33) solution Levine in Detroit uses as high as 60 000 units or 1 cc of 6 per cent solutions Personally I have never used a larger dose than 1 cc of a 3 per cent solution I find larger amounts *unsafe and unnecessary to* give protection

There is some controversy as to whether one can make a stronger extract than 3 per cent (1 33) Piness Huber and Black are of the opinion that stronger extracts are not possible to make Cooke has succeeded in making a 9 per cent extract by evaporation It is questionable whether an extract of this type will actually maintain protein nitrogen three times the amount of a 3 per cent solution My top doses vary from 0 5 cc of a 3 per cent solution to 1 cc of a 3 per cent solution (15 000 to 30 000 units)

The treatment just described is termed the preseasonal and co seasonal method the patient starting his treatment twelve *to fifteen* weeks before the beginning of this particular pollen season For the *perennial form of treatment a sub peak dose is administered at* biweekly intervals throughout the year then gradually increased again preseasonally The two week interval is to be preferred because by this form of treatment constitutional reactions are less likely to occur and a higher peak dose may be obtained

Preseasonal Treatment

This method of treatment is the oldest one used and still has certain indications such as in very mild cases for those patients presenting themselves for the first time for treatment *twelve to fifteen weeks before the onset of their season and for patients for whom* perennial treatment would constitute an undue hardship

One of the shortcomings of preseasonal therapy is that the peak *dosage can never* be raised as high as in perennial treatment the hyposensitization obtained is not as lasting as that gained through perennial treatment and therefore the following season the entire cycle must be repeated starting anew with the low dosage There can be no hope for permanent results by this method the patient can be promised relief for the present season only Another marked

disadvantage is that constitutional and local reactions are more severe because of the short time in which adequate hyposensitization must be achieved It is a general rule that the higher the peak dose the more protection the individual has and it is usually impossible in the limited time available to reach as high a peak dose under this therapy as under perennial management These problems may be illustrated by the following case

Mrs R W age 35 a university instructor was first seen because of a history of hay fever beginning in June intensified around August 15 and remaining until the first frost This patient had had no treatment for several years Intradermal skin tests demonstrated positive reactions to timothy June grass red top and orchard grass and to ragweed short ragweed giant and corn (It is interesting to note that many patients react to corn eaten during the ragweed season with a violent exacerbation of symptoms Corn was eliminated from the diet and treatment was started with 0 1 cc of a 1 10 000 dilution of a grass mixture injected in one arm while 0 1 cc of a 1 10 000 dilution of a 50 per cent short and giant ragweed mixture was given in the other arm The treatment was continued by the dosage of the grass mixture being increased by 0 1 cc every three days until 0 5 cc of this dilution was being used whereupon the same schedule was begun with a more concentrated solution The ragweed dosage could be rapidly increased so that within eight weeks 0 4 cc of the 1 100 ragweed mixture was being well tolerated The grass symptoms were controlled on a repeated dose of 0 4 cc of a 1 1000 dilution given every three days The treatment for the grass was coseasonal and for the ragweed preseasonal Note that the peak dosage obtained in the preseasonal treatment fell far below the optimal desired dose of 0 5 cc of a 3 per cent ragweed mixture Larger doses of ragweed were not attempted because of the occurrence of systemic reactions The patient was placed on perennial treatment at the close of the season

Coseasonal Treatment

This is the term used in describing the therapy given a patient who is already suffering from hay fever symptoms One can certainly afford these patients some relief the severity of the symptoms may be ameliorated and the threat of bronchial asthma may be averted The author prefers to inject 0 1 cc of a 1 10 000 dilution of a pollen extract intradermally either in the forearm or outer surface of the

arm The local reaction ensuing may last for twenty four to forty eight hours at which time the patient returns and 0 15 cc. of the same dilution is given Succeeding injections may be given subcutaneously in larger amounts, reaching within a few days a dose of 0 4 cc of 1 10,000 At this time one may change to a dose of 0 1 cc of a 1 1000 dilution subcutaneously, gradually increasing this amount by 0 1 cc every three or four days until 0 4 cc of this dilution is reached It is rare that one is able to increase the dose still further without danger but frequently the patient will obtain relief by repeating this dose every three or four days for the balance of the season

To illustrate this treatment, a few cases from the author s experience may be cited

H S, a 9 year-old girl came into the office with hay fever symptoms on June 1, with a history of hay fever for the previous three years the attacks lasting from June 1 until October 1 She had received no treatment Intradermal skin tests revealed positive reactions to June grass timothy red top and orchard grass short and giant ragweed and burweed marsh elder She was started on a mixture of the grasses 0 1 cc of 1 1000 dilution increasing by 0 1 cc every third day until 0 5 cc could be given with moderate local reactions Marked relief was obtained from this treatment at a time when the grass pollen count was high and she was successfully carried through the season with 0 5 cc of 1 1000 dilution of grasses injected subcutaneously every three days She was also started on ragweed in anticipation of the coming fall season At the present time, this patient is receiving 1 100 ragweed and burweed marsh elder solution 0 5 cc, and the grass mixture dosage is now 0 3 cc of a 1 100 dilution

H F, a 5 year old boy came in on August 5 with well advanced symptoms of hay fever and cough The mother stated that two nights previously she had heard the patient wheezing as he slept Examination disclosed redness of the eyes nasal obstruction, rhinorrhea and sibilant and sonorous râles over both lungs Intradermal skin tests produced large positive reaction from ragweed giant and ragweed short, and smaller positive reactions to cocklebur Because this boy came in during the season without having had any previous treatment our therapy consisted of an initial intradermal injection of 0 05 cc of a 1 10 000 dilution of ragweed and cocklebur (40 per cent giant ragweed 40 per cent short ragweed and 20 per cent cocklebur) and increases in dosage of 0 05 cc. were made every other day until a dose of 0 15 cc of the 1 10 000 could

be given intradermally The local reaction would persist for some twenty four hours with amelioration of symptoms When 0 2 cc of this dilution could be tolerated, it was given subcutaneously and increased until 0 5 cc of this dilution was being given Treatment was started on August 5 and the latter dose was reached by August 15 Adjuvant therapy was given for the eye and nasal symptoms and considerable relief was obtained by this coseasonal treatment, far more than could be expected by the ordinary use of drugs

Perennial Treatment

The author regards this method as the treatment of choice Perennial treatment consists essentially in the continuation of the treatment given preseasonally and coseasonally with a gradual increase in the dosage at the end of the season The injections are continued once every two weeks throughout the year, gradually increasing the amount and concentration until a high peak dose is reached, such as 0 5 cc *of a 3 per cent pollen solution This method also applies* to the patient who presents himself for the first time after the season The peak dosage once attained is continued every two weeks until the beginning of the season, when it is decreased by ⅓ For example, a patient receiving 0 5 cc of a 3 per cent mixture of ragweed or grass pollen is given 0 35 cc during the season and an attempt is made to continue this dosage providing the local reactions are not too severe It may become necessary to still further reduce this amount, especially when the pollen counts are very high

To illustrate further, the following case may be cited

Mrs W S age 22 who came into the office in February, had a history of severe hay fever with occasional asthma since the age of 12 In addition, during the previous two years she had had increasingly severe nasal obstruction for which an otolaryngologist removed the posterior ends of the inferior turbinates She had been treated since the age of 12 with mediocre results Intradermal skin tests revealed the following positive reactions All the grasses, giant and short ragweed oak and cottonwood trees house dust, orris root, feathers, and sheep wool The first step in the treatment was the elimination of feathers by covering the pillows with special nonpermeable covers and the elimination of contact to raw wool, as in blankets and sweaters Orris root was eliminated by avoiding orris-containing cosmetics and powder Hyposensitization was begun with grasses 0 1 cc of a 1 1000 dilution, oak

and cottonwood 0 1 cc 1 1000 and short and giant ragweed 0 1 cc. of 1 1000 house dust a 1 10 000 dilution of a concentrated house dust extract 0 1 cc.

Grasses and ragweed were injected into the left and right arms respectively at one visit while house dust oak and cottonwood were given the next visit so that only two antigens were given per week The doses were rapidly raised by 0 1 cc until 0 5 cc of this dilution was being given Then 0 1 cc. of 1 100 dilutions were used again increasing by 0 1 cc until 0 5 cc of this dilution could be tolerated At this time she was started with 3 per cent mixtures increasing only by 0 05 cc until 0 5 cc of the 3 per cent mixture was well tolerated This patient for the first time in her history went through the grass and ragweed seasons with almost no difficulty whatsoever

This serves as another illustration of the fact that the pollen sensitive individual is often hypersensitive to other substances and that *it is only by complete testing and elimination therapy that hyposensitization* can achieve really good results

Dr W S age 25 came in March with a history of hay fever and asthma for seven years from August 5 to the first frost During the preceding three years the patient had complained of nasal congestion and asthma in the winter and for the months of June and July as well as August He had received treatment for ragweed sensitivity before consulting me Intradermal skin tests revealed positive reactions to ragweed short and giant to alternaria and hormodendron (molds) and to house dust and feathers Grasses were negative even in a dilution of 1 100 The interesting part of this history was the fact that the most severe symptoms were experienced in the summer during the months of June and July although repeated grass tests were negative It was therefore thought that molds were responsible for the nasal symptoms and asthma during these two months

Treatment was begun by elimination of feathers by means of non permeable pillow covers and by hyposensitization with ragweed house dust and molds gradually increasing the dosage until 0 5 cc. of 3 per cent mixtures and concentrated dust could be well tolerated After six months of therapy nasal symptoms were markedly improved and asthma was noted only infrequently

This case illustrates the diagnostic problems of marked symptoms during the grass season without demonstrable sensitivity to grasses It is particularly in these cases that mold allergy must be considered (see chapter on mold allergy)

Other Factors in Pollen Treatment

It is imperative for hay fever patients to be completely skin tested for associated sensitivities such as mold, house dust orris root, feathers, wool, silk, cotton, and foods This procedure is necessary if one is to reap the full benefit of allergic treatment Obviously, a patient who reacts to feathers as well as to grass pollen will not be completely relieved on grass pollen treatment alone, indeed, contact with feathers will prevent the patient from enjoying the relief otherwise obtainable It must be borne in mind that hay fever patients are prone to show multiple sensitivities, as the author has previously pointed out It is rare to find a hay fever patient sensitive to only one pollen or substance As a matter of fact most hay fever patients have additional sensitivities not only to pollens but to other substances as well Many patients react adversely during their pollen season to certain foods to which they show no intolerance during the rest of the year Other patients can smoke freely during the year but get severe hay fever attacks on smoking during the season

A pollination schedule for many important allergens is given in the Appendix

The major tree pollens are oak cottonwood, ash maple, and elm The minor tree pollens are box elder, walnut, hickory sycamore and tree of heaven The terms major and minor refer to which group of pollens is the more predominant

The major grasses are blue grass, timothy, orchard grass red top, and Canada blue grass the minor grasses are quack grass, and sweet vernal grass

The major weeds are short ragweed, giant ragweed burweed marsh elder, cocklebur, and Russian thistle the minor weeds are lambs quarter, pigweed English plantain, Western water hemp and tall wormwood

Foods such as cantaloupe, watermelon, peaches, and apricots are most likely to intensify symptoms during the season in some patients Complete history taking supplemented by thorough skin testing will point out these variables and aid materially in the treatment of the patient, often spelling the difference between the success and failure of the therapy

Causes of Failure in the Treatment of Seasonal Pollinosis

Incomplete or inadequate testing is one of the most important causes of failure in the treatment of hay fever By not testing completely one may overlook a sensitivity to certain rarer forms of pollen or to orris root feathers cottonseed insecticides or other common inhalants Food sensitivities may likewise be missed as well as dust molds and spores which may additionally be responsible for symptoms In practice one rarely finds a patient affected by pollen only and it is these additional sensitivities which spell the difference between success and failure in treatment Inadequate treatment with pollen extract may also be responsible for poor results and this generally happens when the patient reports too late for the dosage to be raised to an effective therapeutic level or when the treatment is stopped too soon

The extracts used in the treatment may have lost their potency because of exposure to room temperatures or because of aging Potency is lost rather rapidly unless extracts are kept in a refrigerator at temperatures of about 45° to 50° F especially in dilutions of 1 1000 1 10 000 or higher These dilutions must be freshly prepared at least once every two to three weeks 1 per cent and 3 per cent extracts when kept at the proper temperature of 45° to 50° F may keep at least one year without a very appreciable loss of potency

The following case is an example of the necessity of individual treatment

Mr S S age 50 reported hay fever symptoms followed by asthma for thirty years five years of pollen hyposensitization to the giant and short ragweeds gave very little relief from the hay fever or asthmatic symptoms Tests revealed a higher sensitivity to cocklebur pollen than to either short or giant ragweed It was further discovered that cocklebur plants were growing in abundance in the vicinity of this patient s home The treatment consisted of hyposensitization to short and giant ragweed in equal proportions plus injections of cocklebur pollen extract given in the other arm until 0 5 cc of a 3 per cent extract could be tolerated On such a regime this patient experienced almost complete relief from hay fever and there have not been any further asthmatic symptoms

Commercial pollen extracts that are intended to relieve the majority of hay fever patients, regardless of their sensitivity, are of little use in individual treatment When failures occur in over 50 per cent of these patients one may be inclined to place the blame on pollen treatment in general The proper mixture of pollens must be made up in proper proportions, depending on the relative sensitivity of the patient as demonstrated by the skin tests Should tests show a greater sensitivity (larger skin reactions) to burweed marsh elder, for example, than to giant and short ragweed, one should prepare an extract using at least 50 per cent burweed marsh elder, 25 per cent giant ragweed and 25 per cent short ragweed These pollens showing the largest skin reactions should be present in greater proportion in the pollen mixture, while those showing smaller reactions should be in smaller proportions This rule applies to the weeds causing fall or late summer symptoms Tree pollens need not be grouped in *mixtures since patients are usually sensitive to only a single pollen in* the group of oak, cottonwood, ash, maple, elm and tree of heaven, the most common being oak pollen In grass hay fever, a mixture of equal parts of the four or five common grasses is used in treatment

Many observers report positive skin reactions from pollens of plants belonging to the same family or genus This commonly occurs with the various grass pollens, for example, a patient showing a positive skin reaction to timothy may also show a positive reaction to other botanically related grasses such as blue grass orchard grass red top, and Bermuda grass Similar observations have been made with the Compositae group, such as giant and short ragweed, golden rod and sunflower These occurrences are crossed pollen reactions probably due to a basic similarity in the pollen proteins However, sufficient differences exist to give variations in the quantitative response obtained

Some observers have claimed that this is sufficient evidence to treat grass sensitive patients only with timothy pollen instead of with all the grass pollens that show positive reactions It is evident that such a procedure materially simplifies the problem of the commercial preparation of pollen extracts While there is, at times a tendency towards group reactions with pollens and botanically related foods, these occurrences are not constant since some pollens react positively much more frequently than other members of the same family

Grasses that are not widely distributed and whose pollens are, therefore, not abundant, and pollen from plants that shed little, such as wheat, crab grass, and rye, produce few positive skin reactions even though related to the general grass group Similar observations were made among the Compositae group (ragweed short and giant, southern ragweed, western ragweed, false ragweeds, marsh elder, cocklebur, pyrethrum, etc), the chenopods (lamb s quarter and Russian thistle), and the amaranths (pigweed and spiny amaranth)

In practice, best therapeutic results are obtained by testing patients with all the pollens to which exposure occurs and treating with ex tracts of all the pollens to which the individual is actually exposed during the time he has symptoms

Sometimes the patient has only slight relief during the first season following treatment but experiences marked improvement during the second season Most patients obtain better results with each suc ceeding year of treatment and some may reach a point where further therapy is unnecessary This stage may come after three to four successive years of treatment but varies considerably with each pa tient, however, in some patients this stage is unattainable by available methods of therapy

Treatment with Oral Pollens

Many reports of the use of pollen extracts and dry pollen in cap sules by mouth have been made since 1927 Some observers demon strated that the antigen enters the blood and is excreted in the urine and feces Conflicting reports are evidenced on relief of hay fever symptoms by this method of hyposensitization

The author has observed marked gastrointestinal symptoms, such as nausea abdominal pain and diarrhea, resulting from large doses of pollen by mouth The amount of the circulating antigen absorbed from the intestinal tract is infinitesimal as compared to that circulat ing after subcutaneous injection Results in treatment have been poor and do not compare with those following injection of pollen extracts

Precautions to Be Observed in Pollen Injections

Too often the injection of pollen extracts into a patient is con sidered a routine task using a relatively innocuous material It is

important to realize that pollen is an extremely dangerous and highly potent antigen which can cause local and constitutional reactions attaining in certain circumstances a state of complete anaphylactic shock The severity of the constitutional reactions depends on two factors the amount of pollen administered and the speed with which it is distributed throughout the body Dosages must therefore be increased very slowly with considerable attention being paid to the appearance of systemic or severe local reactions Of even more importance is the care which must be exercised as to the route of administration There is great danger that in administering the pollen subcutaneously a small blood vessel may be punctured causing the pollen to be released directly into the blood stream In these cases extremely severe reactions will result almost immediately Great care must be exercised to test whether the needle is in a blood vessel before pushing the plunger home If by accident the injection is given intravenously vigorous countermeasures should be begun immediately These consist of applying a tourniquet above the site of injection and immediately giving from ½ to 1 cc of epinephrine 1 1000 subcutaneously above the tourniquet If severe local or constitutional reactions are not soon controlled it may be necessary to repeat the injection of epinephrine until symptoms disappear The tourniquet should be released after five or ten minutes and should symptoms reappear it may be necessary to reapply it for fifteen or twenty minutes In hot weather when patients are perspiring the increased vascularity of the skin causes a more rapid absorption of the pollen extracts and there is more likelihood of penetrating a superficial blood vessel Under these circumstances even greater precautions should be taken when concentrated extracts are used The patient should be observed in the office for a period of twenty or thirty minutes following the injection

The importance of these precautions can be best shown by the following case Although this author has had only one severe pollen reaction in his experience it is so typical that it may be quoted This patient was relieved of his symptoms but there have been many cases in the literature that have resulted in fatalities

Mr S G age 25 was undergoing hyposensitization to ragweed giant and short. His dosage was 0 55 cc. of a 3 per cent dilution of ragweed

mixture He appeared for regular treatment on a hot August day very much in a hurry and perspiring freely There had been no previous local or constitutional reactions observed in this patient during the course of three years of treatment A subcutaneous injection of pollen was given and within thirty seconds the patient began to groan complained of an inability to breathe and slumped to the floor completely unconscious He showed an extreme pallor cold perspiration on forehead and entire body was pulseless and his respirations had apparently ceased An immediate injection of 1 cc. 1 1000 epinephrine was given intracardially and 1 cc. subcutaneously Artificial respiration was started A rapid thready pulse reappeared and the patient began to breathe As the patient regained consciousness he complained of severe pain in the epigastrium and he felt a strong desire to defecate He began to vomit profusely Shortly after this his condition improved but a relapse soon occurred He began to wheeze and broke out with giant hives Within an hour all symptoms had disappeared and the patient walked out completely relieved

Pollen Filters

As an adjunct to hyposensitization pollen filters are a great advantage By pollen filter we do not mean a contraption which the patient wears in his nose It is an apparatus that fits under an open window It consists principally of a fan and pad of asbestos filter material fitted in a box which is measured for the size of the window By plugging the fan into an ordinary electric outlet the revolving blades of the fan suck air through the filters into the room On hot days a small piece of ice in a pan placed inside the box will cool the air as it is driven into the room providing a fairly efficient air conditioning unit With the doors of the room closed and this type of filter installed the atmosphere in the room will have very few pollen and dust particles present Tests have shown that a good filter will remove between 90 to 98 per cent of the pollen and dust in the air These filters are so simple that any mechanically inclined individual can easily construct one Inasmuch as the majority of patients have their most distressing symptoms at night and in the early morning a night spent in a pollen free room is conducive to complete rest Patients sleeping in such quarters frequently get through the day very comfortably This arrangement plus hyposensitization offers the best combination of therapy available and even facilitates the

hyposensitization treatment (Any air conditioned room which effectively filters pollens and cools the room is highly beneficial)

Hay Fever Resorts

Occasions may arise particularly in the ragweed season when it is desirable that a patient be in as pollen free an area as possible This necessity rarely arises in grass and tree sensitive patients because of the shorter seasons and smaller amounts of pollen which they experience and because coseasonal treatment is relatively more effective in these cases In ragweed pollinosis however, a patient who is first seen with symptoms in the season may have to be removed either because of the severity of the symptoms or because of complicating asthma

Often a lake or ocean voyage (virtually no pollen is found in the air above large bodies of water) may be highly beneficial for such a patient If preferred the following localities which have a smaller amount of ragweed pollen than most regions are popular resorts

Eastern United States
- Adirondack Mountains and Lake regions
- White Mountains of New Hampshire
- Lake Placid New York
- Coast of Maine especially eastern and northern parts
- Region north of the Saint Lawrence River
- Lower Saint Lawrence valley

Southeastern United States
- Florida

Midwestern United States
- Lake Superior regions
- Mackinac Island Michigan
- Petoskey Michigan
- Saulte Ste Marie Michigan
- Duluth Minnesota
- Eagle River Wisconsin

Western United States
- Rocky Mountains
- Colorado Springs Colorado
- California

Foreign Countries
- New Brunswick

Nova Scotia
Labrador
Quebec, Canada
Banff and Lake Louise, Canada
Europe has very little ragweed

Chapter V

Perennial Hay Fever

Perennial hay fever is known by various names such as vasomotor rhinitis hyperesthetic rhinitis allergic rhinitis, and all year round colds" The symptoms of perennial hay fever are the same as those of seasonal hay fever, namely, sneezing and nasal discharge alternating with periods of partial or complete stoppage of the nose The sneezing and watery nasal discharge are usually worse in the morning whereas the nostrils are more likely to close up at night

SYMPTOMS AND SIGNS

The nasal symptoms of hay fever are usually accompanied by eye symptoms such as watery discharge, itching burning, and redness of the eyeballs and lining of the eyes Itching of the eyes, of the nose, the roof of the mouth and deep in the ears is characteristic of the true allergic type of hay fever In addition to the local symptoms, a feeling of depression, lassitude, or even prostration is frequently complained of

Hansel lists changes in the nose and sinuses as

1 Thickening, hyperplasia, and polypoid degeneration of the epithelium

2 Eosinophilic infiltration of the tunica propria

3 Edema, round cell infiltration and connective tissue proliferation

4 Compression, dilatation and atrophy of the glands

5 Round cell and connective tissue proliferation in the periosteal layers

6 Hyperplastic and rarefying or atrophic processes in the bone

Most of these changes occur in the tunica propria Eosinophilic infiltration is a prominent finding The eosinophils are so numerous in the tissues that they escape into the nasal secretion Similar changes occur in the sinus membrane

The mucosa appears swollen boggy and grayish white in color with or without polyp formation Polyps are more frequently found over the middle turbinates particularly the lower margins anterior tips and anterior ethmoid regions Polyposis and edema may occur in the sinuses although the ethmoids and antra are most frequently involved

The formation of polyps is due to marked edema with prolapse of the mucous membrane They may be unilocular or multilocular and consist of plasma cells eosinophils lymphoid cells and mononuclear cells The outside of the polyp is composed of stratified columnar epithelial cells or flattened cells due to stretching The pedicle is usually connective tissue and there may be associated atrophic or hyperplastic bony changes in the region of the middle turbinate and ethmoid cells

When secondary infection occurs neutrophilic infiltration with connective tissue formation and fibrosis results The eosinophils are temporarily replaced by polymorphonuclears but when the infection clears up eosinophils once more predominate

It is generally believed that nasal mucous polyps are invariably allergic

Allergic Facies and the Allergic Salute

Duke was the first to call attention to the characteristic facial deformity in chronic nasal allergy The malar prominences are flattened resulting in a flat appearance of the face Wasson believes this to be due to underdeveloped sinuses resulting from chronic nasal congestion Bowen and Balyeat call attention to the so-called adenoid facies as an indication of allergy The overriding upper incisors and the V shaped palate form a Gothic arch This type was found in 24 per cent of 100 children who had chronic nasal allergy and in only 5 per cent of 400 controls

Bowen and Balyeat have also called attention to two mannerisms characteristic of nasal allergy in children The first is nose rubbing

or the allergic salute, produced by passing the palm of the hand vertically along the tip of the nose while pressing inward toward the face This is done to promote aeration in the nose and alleviate itching

The second mannerism is nose wrinkling The upper lip is drawn to one or both sides and upward, thus spreading somewhat the ala nasae A short sniffing inspiration may accompany this gesture

DIFFERENTIAL DIAGNOSIS

There are several conditions which may be confused with perennial hay fever Especially troublesome are recurrent head colds, sinus infection and nasal trouble due to reflex or mechanical causes

Recurrent head colds always run a somewhat definite course, frequently starting with a burning sensation in the back of the throat, followed in twenty four hours or less by sneezing and running *of the nose At first, the nasal secretion is thin, clear, and colorless* and is irritating to the skin around the nose and upper lip This secretion later appears thicker and yellowish, thus becoming pussy or mucopurulent

Head colds commonly affect the throat, larynx, and bronchial tubes, thus producing sore throat, hoarseness, cough, and expectoration, in addition to the nasal symptoms These latter symptoms never occur in uncomplicated cases of hay fever A cold continues uninterruptedly for an average period of one or two weeks until it has run its course, whereas attacks of perennial hay fever may come and go suddenly within the space of a few hours The nasal secretion in hay fever remains thin, clear, and colorless throughout unless a complicating bacterial factor is present Furthermore, this watery secretion is definitely less irritating to the skin than is the secretion in ordinary colds The itching of the eyes nose, roof of the mouth, and ears which is commonly present in hay fever, is absent in colds Colds are frequently accompanied by fever, malaise, loss of appetite, headache, and aching of the back and limbs In uncomplicated hay fever, the temperature is usually below normal, although children may have fever with allergic rhinitis or asthma

The following is a chart indicating the differences between allergic rhinitis and head cold

Differential Diagnosis of Allergic and Infectious Conditions of the Upper Respiratory Tract in Children*

Allergic	*Infectious*
HISTORY	
1 Attacks usually recurrent	1 Attacks usually single
2 Often mild symptoms	2 Usually clears up completely
3 Definite relation to heredity	3 No relation to heredity
4 *Not contagious*	4 *Contagious*
5 Not related to exposure to another patient	5 Definite relation to exposure to another patient
6 Constitutional symptoms slight	6 Constitutional symptoms more marked
7 *Foods and inhaled substances* often traced as causes	7 *No relation to foods or inhaled* substances as cause
8 Itching common	8 No itching
9 Wheezing common	9 No wheezing
10 Other allergic conditions present or in past history	10 Usually no other allergic condition present or in past history
EXAMINATION	
1 Visible mucous membranes, pale, glistening, edematous	1 Visible mucous membranes hyperemic, red
2 Thin, watery mucoid nasal discharge, mucoid sputum	2 Mucopurulent or purulent nasal discharge and sputum
3 Smear shows eosinophils, 10% or more	3 Smear shows polymorphonuclear *neutrophils as predominant* cell, eosinophils few or absent
4 Other signs of allergy often present	4 No other signs of allergy
5 Sinus involvement of hyperplastic type	5 Sinus involvement of purulent type
6 Wheezing breath sounds	6 No wheezing breath sounds
7 Roentgenogram shows bronchial markings increased	7 Bronchial markings not increased in roentgenogram
8 Allergic skin reactions usually positive	8 Allergic skin reactions usually negative

TREATMENT

1 Epinephrin specific for treatment	1 No relief from epinephrin
2 Avoidance of specific allergens followed by relief	2 Avoidance of food or inhalant substances produces no change

* Cohen M B and Rudolph J *J.A.M.A* 97 980 1931

In sinus infection, pain and tenderness is usually present over the frontal or maxillary sinuses Fever may accompany this infectious process, and there is usually a leukocytosis X ray films reveal typical cloudy defects of the paranasal sinuses These symptoms do not occur in uncomplicated hay fever Sinus patients with hay fever usually complain of an unpleasant odor and taste, with a drainage of pus from the nose into the throat

A deviated nasal septum making contact at one or more points with the turbinates may produce symptoms simulating nonseasonal hay fever, such as sneezing clear nasal discharge, and stoppage of the nose However, there is an absence of the itching of the nose, eyes roof of the mouth, and ears which is so frequently present in hay fever Intranasal examination reveals the deviated septum and confirms the diagnosis

X ray of the sinuses should be carried out in all cases of allergic rhinitis This is important to rule out empyema which if present would necessitate treatment by an otolaryngologist

Some degree of cloudiness of the sinuses may indicate a thickened membrane, polyps or merely mucous secretion Polyposis may be found on x ray or polyps in a sinus may be recognized Kern and Schenk do not rely on transillumination to diagnose polyps or mucus in the sinuses

Huber and Harsh found 70 per cent of vasomotor rhinitis to be allergic in origin My own observations would place this figure even higher—85 per cent Since the majority of these patients consult the otolaryngologist first for nasal symptoms one is impressed with the desirability for closer cooperation between the allergist and the nose and throat specialist In this way better results can be expected

Primary allergic conditions are often secondarily infected Cure depends on recognition and relief of the allergy The body then

overcomes the infection in most cases This does not preclude treatment for the infection when indicated

ETIOLOGY

Although perennial hay fever, like bronchial asthma, may be due to a variety of causes, a carefully taken history will frequently supply invaluable information about the offending substance or substances In this connection, the old proverb may be paraphrased to read, 'The hair of a dog is sometimes worse than his bite" Not infrequently, patients state that petting a cat or being around horses produces symptoms of hay fever Skin tests performed in such cases confirm the fact that such persons are sensitive to the hair and dander proteins of the offending animals

When persons with perennial hay fever find their symptoms aggravated by scented face powders, body talcums, or sachets, the possibility of sensitization to powdered orris root, a common component of cosmetics, is quite strong A violent sneezing spell following a dry shampoo is practically conclusive evidence that the patient is sensitive to orris root

One patient in my experience invariably had a violent attack of hay fever whenever she applied hair-curling liquid She was found sensitive to flaxseed, which is an ingredient of all curling fluids When use of the curling fluid was discontinued the hay fever symptoms disappeared

In perennial hay fever as in bronchial asthma, inhalant or airborne substances are far more important than those taken orally, such as foods and drugs Nevertheless, the possibility of sensitivity to food must not be overloked in studying such patients When perennial hay fever is due to food sensitivity there are likely to be other symptoms referable to the stomach, intestinal tract or skin Symptoms which indicate sensitivity to foods are swelling of the lips itching or constriction of the throat, nausea vomiting, abdominal pain, diarrhea, itching of the skin, or hives especially if the symptoms characteristically follow the eating of any particular food

A complete history of the patient's physical environment, occupation, and activities is all important in determining the etiologic substances responsible for symptoms In obstinate cases a visit to the

patient's home or place of work may often give a clue as to the causative factors

My personal experience coincides with that of Gelfand, who finds some specific single or multiple sensitivity in about 85 per cent of this group of patients In some 15 per cent, various nonallergic factors are the cause of the rhinitis Changes in temperature, endocrine dysfunctions vapors gases, smokey atmospheric conditions, odors of lacquer, turpentine, paint, varnish, and dyes, cooking odors, colognes and perfumes, chemical irritants such as acids, ammonia, essential oils physical agents as cold, heat, dampness rain chilling or overheating of the body—all are causative agents In the allergic group, inhalants and foods or a combination of both may be found responsible for symptoms and they can be demonstrated by skin tests

Patients may become sensitized to materials used in their occupation after repeated contact or may have been previously sensitive to these substances Food handlers in grocery stores, restaurants, and warehouses may become affected by inhaling dust from sacks of peas and beans (Wittich) fumes of coffee (Steinberg and Sorrell), or dust from cocoa beans and chocolate Inhaling spices such as paprika has been reported by Gelfand to cause perennial hay fever

In bakers wheat buckwheat, rye, and barley flour may be responsible allergens Poultry handlers, butchers, and farmers are exposed to feathers and linseed meal Furriers come in contact with animal hairs and skins such as rabbit, cat fur, cowhide raccoon muskrat, fox persian lamb mink, and seal The dyes used on these skins may also in time cause a nasal allergy The commonly used fur dyes paraphenylenediamine or Ursal D and para aminophenal (Ursal P) are largely responsible for the production of symptoms Pharmacists and laboratory workers may become sensitized to the drugs and chemicals they handle such as caroid lycopodium, ipecac, peptone, and rhubarb Kern reports a patient, a laboratory worker, who was sensitive to a simple chemical phthalic anhydride Scratch tests resulted in a positive reaction and passive transfer tests were likewise *positive*

Following is a list of some common agents causing perennial hay fever A more complete list of inhalant ingestant, and contact allergens will be found in the Appendix

Animal group
Dog hair
Cat hair
Rabbit hair
Cattle hair
Horse dander
Chicken feathers
Duck feathers
Goose feathers
Sheep wool
Horse serum

Drugs
Aspirin
Pyramidon
Quinine
Caroid
Lycopodium
Pepsin
Procaine
Ephedrin
Sulfa group

Miscellaneous group
Orris root
House dust
Cottonseed
Linseed or flaxseed
Silk
Wool
Mattress dust
Kapok
Soaps
Paints—turpentine
Cooking odors

Foods
Wheat
Eggs
Milk
Cereals
Condiments

Meats
Beef
Pork
Chicken
Lamb
Veal

Vegetables
Broccoli
Beets
Cauliflower
Cabbage
Carrots
Lettuce
Onions
Potatoes
Radishes
String beans
Spinach
Tomatoes
Yeast

Molds
Alternaria
Hormodendron
Aspergillus fumigatus
Penicillin

DIAGNOSIS BY SYMPTOMATOLOGY AND TESTS

Much of the symptomatic information necessary for the diagnosis of perennial hay fever has been covered in the previous discussion There are, in addition, several technics employed in the differential diagnosis of the offending allergen

SCRATCH AND INTRADERMAL TESTS

To confirm the diagnosis scratch and intradermal skin tests are made Certain precautions must be observed in intradermal skin tests in perennial hay fever In testing to cottonseed and flaxseed particularly, intradermal tests with the usual dilute extracts may produce severe local and constitutional reactions It is advisable to test with these substances by using a dilute solution such 1 10 000

as a scratch test first, if the scratch test is negative then an intradermal test may be done using a 1 100 000, 1 50,000, or 1 10,000 solution For example, a 7 year old girl with perennial rhinitis and a complicating asthma would get severe local reactions and severe asthmatic symptoms following a scratch test with a 1 10 000 dilution of a cottonseed extract Large positive intradermal tests were obtained by the intradermal injection in this patient of a 1 1,000 000 dilution These same precautions should be followed with horse dander, house dust, and linseed

In the inhalant group, the following allergens are important and should be used in the following dilution in testing

Dog dander, 1 100 dilution
Cat dander, 1 100
Horse dander, 1 1000
Horse serum, 1 1000
Cottonseed, 1 10 000 or greater
Flaxseed 1 10 000 or greater
Lycopodium, 1 100
Silk, 1 25
Cow hair, 1 100
Animal hair, 1 1000
Rabbit dander, 1 25
Wool 1 25
Glue (furniture), 1 100
Kapok, 1 100
Tobacco 1 50
Fungi—yeasts molds, 1 1000

The important foods that should be used in testing are

Egg white 1 50
Milk 1 10
Wheat, 1 10
Beef, 1 100
Pork, 1 100
Shrimp, 1 200
Orange, 1 10
Paprika, 1 100
Green pepper 1 100
Banana, 1 100

Chocolate, 1 25
Buckwheat, 1 100
Peanuts, 1 50
Tomato, 1 10

In the interpretation of skin tests to foods, it should be remembered that they are more likely to be positive in children In adults a suspected food may fail to produce a positive skin reaction and never theless be the cause of symptoms For this reason, it is sometimes wise to use elimination diets in conjunction with skin tests (see section on elimination diets in the Appendix)

Intranasal or Sniff Test

As a further adjunct in the diagnosis of perennial rhinitis a small amount of the suspected substance may be placed in the nose and the local intranasal reaction observed It is often a simple diagnostic procedure to place a small amount of the patient's powder, for instance, over one of the inferior turbinates and note the onset of sneezing, watery discharge, and local tissue swelling which usually appears in a very few minutes Dr Noah Fabricant, by personal communication with the author, describes a severe perennial rhinitis in which the etiologic agent was a geranium perfume in a face powder This was diagnosed very conveniently by the sniff test

Technic of Nasal Smear for Demonstrating Eosinophils

The patient is instructed to blow the nose into waxed paper or a cellophane handkerchief The mucoid material is spread thinly on a microscope slide and fixed with heat Wright's or Giemsa's stain* is used, as in a differential blood smear With Wright's stain, the coarsely staining granules in the leukocytes are red in color, whereas with Giemsa's stain, they are brownish red with a blue nucleus

The Giemsa stain technic is probably the simplest technic to use in demonstrating eosinophils One drop of stain is diluted with 1 cc of distilled water About 1½ cc is required for each slide The smear should be fully flooded with the stain and allowed to remain for twenty five to thirty minutes Pour the stain off and gently dip the slide into distilled water Add a few drops of ethyl alcohol to clear

* Giemsa's stain may be purchased from Gradwohl Laboratories in St Louis Mo

the excess stain Stand slide on end for a few minutes to drain and dry Examine slide first under the low power of the microscope then the high power or oil immersion

TREATMENT

The first step in the treatment of perennial rhinitis is the etiologic diagnosis and elimination of all offending substances in so far as possible It is of the utmost importance to hyposensitize these patients to the inhalant substances which cannot in most cases be avoided Hyposensitization to foods is generally ineffective

Change of occupation may have to be considered where continual exposure occurs and where hyposensitization is not feasible In cases of animal sensitivities it is urgent for those animals or pets to be removed from the patient s environment

Local therapy should be essentially the same as that for seasonal pollinosis

The following prescription may be useful in severe nasal blockage after privine or tuamin have been used unsuccessfully

Epinephrin 1 1000 (4 cc)
Ephedrine 3% in normal salt sol (30 cc)
S g Few drops in nose every 4 hours as needed

One must avoid nasal surgery or any other local irritating treatment such as packs and concentrated astringents for in my experience these have done more to aggravate the condition than to help it If nasal polyps or extreme hypertrophy of the turbinates occur the nasal surgeon may remove the polyps and the posterior ends of the inferior turbinates

Dangers of Surgical and Local Treatment in Perennial Hay Fever

Patients with perennial hay fever are often seen who have had either nasal packs or some operative procedure such as removal of the septum or a turbinectomy These procedures were performed by otolaryngologists for relief of nasal congestion The results obtained by these measures are uniformly poor and have often led to further complications These measures were doomed to failure since the essential cause of the difficulty was primarily allergic The body

responds to the removal of one sensitive tissue by showing an increased sensitivity in another responsive tissue Thus the complications of surgical treatment of the allergic nose appear as asthma and increased nasal turgescence in nontreated areas of the mucosa which previously showed no allergic response In addition the factor of operative trauma greatly increases the sensitivity of the nasal structure

Treatment of Inhalant Allergies Other Than Pollen

The most important allergens to which we are exposed daily throughout the year are the following house dust, feathers, orris root, pyrethrum castor bean dust, tobacco smoke, kapok, fish glue, silk, and animal emanations Exposure to fungi and yeasts occurs less frequently

In general, avoidance and hyposensitization are of the utmost importance

Pets should be removed from the environment, feather pillows covered with an impervious covering mattresses covered and house dust precautions instituted

House Dust The specific allergen in house dust has not been identified but there is evidence that it is present in old mattresses, pillows upholstered furniture draperies rugs curtains and automobile upholstery The deterioration of old cotton, cotton linters and kapok results in a fine brownish powdery substance which acts as a very potent allergen in susceptible individuals

It is one of the most common causes of perennial rhinitis and asthma Dust picked up from the floor or street dust are of minor importance

The present opinion seems to favor the theory that some enzyme action or mold breaks down the cotton, cotton linters or kapok mattresses and overstuffed furniture with the resulting fine brownish powdery irritant

To overcome this a new mattress may be substituted and many patients are relieved of symptoms almost immediately

Nonallergic dust proof coverings may be used on pillows and mattresses All rubber mattresses made of sponge rubber are also available and are excellent for dust sensitive patients Pillows of sponge rubber can also be purchased

To obtain autogenous dust, the bag is removed from the vacuum cleaner and a small piece of cloth is tied around the outlet The vacuum cleaner is then run over pillows, mattress, articles of up holstered furniture, and draperies It is not necessary to obtain more than one or two teaspoonsful of dust in this way

Extracts made of this dust are quite potent Dust sensitive patients should use vacuum cleaners that blow the dust through water

Dosage of House Dust Extract

Dilution		
1 10 000	No 1	0 1 cc
	No 2	0 2 cc
	No 3	0 3 cc
	No 4	0 4 cc
	No 5	0 5 cc
1 1000	No 6	0 1 cc.
	No 7	0 2 cc
	No 8	0 3 cc
	No 9	0 4 cc
	No 10	0 5 cc
1 10	No 11	0 1 cc.
	No 12	0 2 cc
	No 13	0 3 cc
	No 14	0 4 cc
	No 15	0 5 cc
Concentrated dust extract	No 16	0 1 cc
	No 17	0 15 cc.
	No 18	0 20 cc
	No 19	0 25 cc.
	No 20	0 30 cc
	No 21	0 35 cc
	No 22	0 40 cc
	No 23	0 45 cc
	No 24	0 50 cc

Dilutions are gravimetric volumetric.

Increases may be made until 1 cc can be tolerated At first, the injections are given every three to five days but when a concentrated

extract is given injections once a week are sufficient After a dose of 1 cc of concentrated dust extract is tolerated injections are given at longer intervals once in two or three weeks so that the tolerance which has been built up may be maintained Injections may be completely stopped when local reactions disappear following injection of the concentrated extracts and symptoms are under control The time when this point is reached varies with each individual patient

Instructions for House Dust Avoidance If you are house cleaning or if you are at home during cleaning hours cover your nose with moistened absorbent cotton held in place by a piece of cheese cloth or 4 ply gauze This will prevent sneezing during cleaning Use only a vacuum cleaner

Stuffed furniture should be removed or covered with nonallergic dust proof fabric under the frieze material Bedrooms should contain as little furniture as possible Washable wooden chairs are advised

Rugs are dust-catchers and should be removed Use linoleum or small washable scatter mats Discard draperies heavy curtains pictures and other dust catchers Use only washable blankets spreads and curtains and wash at least once a week

Wash wooden furniture with soap and water making sure to clean the top bottom front back inside, and outside and cover with sheets until all cleaning is completed Wash the woodwork Clean walls and closets removing dust-catching articles Clean moldings with oiled or damp cloth Spray closets with antiallergic insecticide Wash radiators and seal radiator and pipe openings Wash and wax floors

Beds should be scrubbed and sprayed with antiallergic insecticide containing no pyrethrum Clean the springs and slats thoroughly If more than one bed is in the room both should be taken care of as suggested

Mattresses pillows and box springs should be covered with non allergic dust proof coverings The coverings should be appreciably airtight so that no dust can come through

Clean the bedrooms daily and give room a thorough cleaning at least once a week Use a damp cloth when dusting The room should be for sleeping only

Permit no pets or animals

Keep away from that part of the house that is being cleaned Avoid contact with strong odors coming from gasoline, paint varnish fumes smoke perfume Avoid contact with dust Give children washable toys

Feathers Feather pillows usually consist of duck goose or chicken feathers or a combination of the three

Feathers are also found in comforters and overstuffed furniture The bedroom should be made free of all feathers Pillows should be covered with a nonallergic cover or better yet a sponge rubber pillow should be purchased Overstuffed furniture is not permitted in the room

Kapok is a poor substitute for feather pillows since patients may become sensitized to this substance

Directions for the Avoidance of Feathers

1 Remove all feathers from the house and store feather pillows and comforters in sealed or moth proof bags

2 Wash floors and woodwork

3 Go over furniture picture molding bed slats bed springs and backs of pictures with an oiled or damp cloth

4 Use sponge rubber pillows and mattresses or kapok pillows if the patient has been tested for sensitivity to kapok

5 If feather pillows must be used cover them with nonallergic rubberized coverings

6 Do not use feather comforters

7 Permit no draperies or rugs in the patient s room

8 Clean the entire house with a vacuum cleaner

Orris Root Orris root may be found in perfumes scented soaps and face and talcum powders It is widely used in the cosmetic industry because of its flesh color and pleasant odor It acts as a mordant for perfume and colognes thereby retaining the odor It may be found in shaving creams bath salts tooth powders and hair tonics Tincture of orris is often present in skin creams foundation creams and lotions and sun tan lotions A list of common cosmetic irritants and allergens is given in the Appendix

The following powders and cosmetics do not contain orris root Marcelle Frost s Armands Ar Ex Hypo Allergenic Mansfield and Almay products

Dosage Schedule of Orris Root Hyposensitization

Dilution	
1 25	0 1 cc
	0 2 cc.
	0 3 cc
	0 4 cc
	0 5 cc
1 5	0 1 cc
	0 2 cc
	0 3 cc
	0 4 cc
	0 5 cc.
	0 6 cc.
	0 7 cc.
	0.8 cc.
	0 9 cc
	1 0 cc

The doses are increased as rapidly as possible preferably every four to five days Continue with 1 cc doses once in one or two weeks These dilutions are gravimetric volumetric A 1 5 dilution means 1 gm of pure orris root in 5 cc of diluent

Pyrethrum Pyrethrum is the dried powdered flower of the pyrethrum plant and a close member of the chrysanthemum family It is used in sprays and powders as an insecticide It is often used to moth proof carpets draperies and furniture in homes and theaters Severe rhinitis and asthma may follow exposure to this substance

If upholstered furniture rugs and draperies have been moth proofed they should be thoroughly aired out of doors before being used in the house

There is an insecticide spray specially prepared for persons sensitive to pyrethrum or rotenone that is called Kilit This substance is practically odorless and appears to be effective in controlling any of the ordinary household pests

Since complete avoidance is not always possible hyposensitization is required to the extract of pyrethrum as with orris root or dust Satisfactory results are obtained Pyrethrum extract frequently gives positive skin tests in patients sensitive to ragweed and contact should be avoided especially during the season

Castor Bean Dust Figley and Elrod reported a series of 30 pa

tients with rhinitis and asthma who worked in a Toledo castor oil mill or lived within a mile of the mill Symptoms were caused by inhalation of the fumes of the castor bean dust

Bennett Schwartz Ratner and Gruehl showed that the oil is non allergenic but the dust is extremely so In testing to this substance the scratch method is recommended and hyposensitization should be carried out with very minute doses and cautiously

Tobacco Inhalant allergy to tobacco smoke occurs approximately in 1 per cent of asthma patients but is probably more common *in perennial rhinitis The tobacco may cause contact dermatitis* Gum tragacanth arabic glucose and corn syrup are frequently used in cigars

In making tobacco smoke extract the simplest method is to hold the lighted cigarette or cigar to the end of a rubber tubing attached to a suction pump The smoke is drawn into an attached flask containing the dextrose extracting fluid and then filtered through a Seitz filter The concentrated extract is then diluted ten times for intradermal testing It may be used full strength for scratch tests

Kapok Kapok is obtained from the pods of the silk cotton tree (Bombacaceae) which grows abundantly in the West Indies and Central and South America Brown points out that people allergic to cottonseed are frequently sensitive to kapok but kapok sensitivity almost always accompanies cottonseed sensitivity Kapok is of importance in that the house dust allergen is formed during the aging process probably caused by contamination with molds or bacteria

Fish Glue Le Page glue is chiefly fish glue and is extremely allergenic It is used in furniture shoes boats and labels Postage stamp glue is made from sweet potato;

The scratch test only should be used because patients are usually exquisitely sensitive and several deaths following an intradermal test have been reported These patients are usually fish sensitive

Hyposensitization is risky and not advised

Perennial Hay Fever Resistant to Hyposensitization

There are certain allergens to which the patient responds so violently that hyposensitization would be a dangerous procedure These are cottonseed flaxseed and in some cases horse dander The toxicity of cottonseed and flaxseed in a sensitive patient has been discussed by the author elsewhere These substances function as

inhalant and ingestant factors Injection of even minute amounts of these allergens results in violent local and systemic reactions

Cottonseed

M B, a girl 8 years of age, had asthma due to cottonseed An intra dermal injection of 0 1 cc of a 1 1,000,000 extract of cottonseed in variably resulted in a severe local reaction and an attack of asthma It was impossible to attempt hyposensitization in this girl because of the severe asthma which would follow each treatment It was more feasible to control asthmatic symptoms by completely eliminating cottonseed from her environment

Cottonseed is found widely distributed in a number of edible and volatile substances As an inhalant, it is found in cotton mattresses, pillows, overstuffed furniture, impure cotton, automobile upholstery, miniature golf course flooring, and in household paints As an in gestant it is present in hydrogenated cottonseed oils used in cooking such as Crisco, Spry, Wesson Oil, and Cottolene Many preparations are made with these oils such as potato chips, french fried potatoes pies, cakes candies, and sardine oil Canned fish such as salmon or tuna may be put up with this oil and it is also found in green olives It is often used medicinally in liniments and ointments Camphor ated oil contains at least 50 per cent of cottonseed oil Patients allergic to cottonseed are often sensitive to flaxseed also Sensitivity should also be looked for to other seeds such as kapok, nuts, lentils peas, and beans These substances could possibly cause symptoms due to crossed reactions because of the similarity of the protein *molecules It is therefore important to completely* eliminate all offending substances from the patient's environment

Individuals sensitive to cottonseed usually give immediate violent allergic reactions when exposed either by inhalation or ingestion to cottonseed meal or protein Usually profuse sneezing, coryza, itching and nasal obstruction occur, with injection of the conjunctivae and lacrimation Severe asthma may follow Urticaria with angioneurotic edema may occur at the same time Severe gastrointestinal symptoms such as vomiting, diarrhea and generalized abdominal pain may follow ingestion of cottonseed flour or meal

One of my patients, a boy aged 10 who was sensitive to cottonseed, developed severe rhinitis and asthma within ten minutes of exposure

to a fertilizer used on the lawn A scratch test made with a small amount of the fertilizer on the anterior aspect of the forearm resulted in a violent local reaction with pseudopodia and flare

The fertilizer contained cottonseed protein and upon inhalation resulted in severe allergic symptoms in this boy who had a known cottonseed sensitivity

Bernton Spies and Stevens were the first to isolate a water soluble fraction from cottonseed composed primarily of a protein and polysaccharide They called this fraction CS 1 and attributed its allergenic properties to the protein component From CS 1 they also extracted a carbohydrate free picrate with similar powerful allergenic properties Bernton and his co workers and Figley are of the opinion that cottonseed oil does not contain these fractions Therefore patients sensitive to cottonseed protein do not react to the oil

The principal vegetable oils for edible use in addition to cottonseed are soybean corn and peanut The oils are obtained by hydraulic presses applying pressure to the seeds or by extracting the oil with a solvent The solvent extraction of the oil probably results in complete elimination of the protein whereas the pressure method may not remove all the protein

Patients sensitive to cottonseed protein failed to show clinical sensitivity to edible cottonseed oil or hydrogenated cottonseed oil such as Crisco Spry Cottolene and Snowdrift when ingested according to the experiments of Bernton et al and Figley Cazort made the same study with corn oil and corn meal on 2 patients who reacted strongly to corn meal but gave no reaction to the oil following skin tests and ingestion of the pure corn oil Figley believes that it is the cottonseed meal or flour as used by the baking industry that produces symptoms It may be used in minor proportions in doughnuts cookies fig bars and occasionally to harden the chocolate in chocolate coated candies

In my own experience I have found cottonseed to be an important factor in 5 3 per cent of 246 asthma patients studied Unger finds the incidence to be 3 3 per cent in 213 patients with asthma

At present there is some disagreement on whether cottonseed sensitive patients are also affected by the oil There are many reports in the literature on symptoms caused by Crisco (Rappaport) Cot

tonseed oil (Rowe) Crisco (Unger) and hydrogenated cottonseed oils by the author

In dealing with these patients complete elimination of these products by inhalation is advised A cotton mattress may be completely covered with rubberized sheeting, or horsehair, kapok, or wood fiber mattress substituted provided tests show no sensitivity to these substances Foam rubber mattresses are also available Remove cotton blankets overstuffed furniture padded with cotton, stuffed dolls, and other toys that may be impregnated with cotton seed

By ingestion, one may attempt to feed cottonseed oil or the hydrogenated oils and watch for symptoms

Case Reports

M F, a pharmacist, age 35 complained of severe attacks of sneezing running nose, and nasal obstruction that occurred only in the pharmaceutical laboratory Skin tests were uniformly negative and a complete inventory was taken of the substances worked with It was found that whenever he handled the pancreatic ferment Taka Diastase he would get a severe attack of sneezing Skin tests to Taka Diastase were negative This case illustrates a very important aspect of the diagnosis of perennial rhinitis the fact that many drugs and complex organic substances do not produce a positive reaction in the skin but do produce symptoms and that the only reliable way of making the correct diagnosis is to reproduce the symptoms with the suspected substance after taking an exhaustive inventory of substances with which the patient comes in contact This patient was completely relieved of all symptoms by avoiding contact with Taka Diastase

Mrs E V, age 55, came into the office with the symptoms and history of a perennial rhinitis of several years duration There was complete nasal obstruction which was resistant even to the local use of epinephrin Skin tests revealed positive reactions to orris root and house dust A change in cosmetics and hyposensitization to orris root and house dust markedly alleviated the nasal symptoms, however, it was then discovered that her husband used talcum powders and after shaving lotions which caused the patient to sneeze violently Elimination of this factor resulted in complete relief of all symptoms

Mrs L J, age 25 had been treated for the past few years for 'sinusitis by many otolaryngologists The patient stated that she had had sneezing and nasal congestion ever since she could remember, throughout the years, and that after a few attacks of sneezing she would experience nasal

congestion and would notice a yellow green nasal discharge the following day She stated that previous local treatment had aggravated the condition and made her worse Skin tests were positive for house dust, orris root, feathers, dog hair, sheep wool, egg white, beets, and cauliflower At the time of our examination, the nasal mucosa was whitish gray and scarred, and the turbinates were hypertrophied and edematous

Treatment was begun by eliminating as much as possible both the inhalant and food reactors, and by hyposensitization to house dust and orris root Local and general symptoms have almost disappeared, and there is no sign of infection of the paranasal sinuses This case illustrates the mechanism by which a long standing allergic rhinitis can be complicated by superimposed bacterial infection, and how, if cognizance is not taken of the allergic factor, treatment may be directed at the complication without thought of the primary etiology

Mrs G F, age 36, consulted me because of sneezing, itching of the nose, watery nasal discharge, asthma, and abdominal pain Sneezing, nasal obstruction, and watery nasal discharge had been present for ten years Itching of the nose and eyes accompanied these symptoms, which occurred throughout the year During the four and one half years previous to seeing me she experienced diffuse abdominal colicky pain accompanied by frequent loose stools containing mucus

Various attacks of urticaria, angioneurotic edema, and swelling of the tongue had occurred during the previous five years

Asthma began sixteen months before and would occur at irregular intervals throughout the year

In the family history, her mother had asthma, her father had hay fever and asthma, one cousin had eczema, and one cousin had asthma One of the grandmothers suffered from some allergic disturbance

During childhood, this patient experienced frequent spells of vomiting after eating She had been examined by several physicians who at one time or another had suspected gallbladder disease, appendicitis, achlorhydria a spastic bowel, and vitamin deficiency X ray studies of the gall bladder, stomach and colon were reported negative except for a spastic colitis This patient was referred to the author in September, 1943, for an allergic survey Intradermal tests were done with the following results

Inhalants, positive tests

Camel hair, 4 plus
All feathers, 4 plus
House dust, 4 plus
Silk, 2 plus
Tobacco, 2 plus

Alternaria, 2 plus
Hormodendron, 2 plus
Birch pollen, 3 plus
Tree of heaven pollen, 2 plus

Foods, positive reactions
Oatmeal, 2 plus
American cheese, 1 plus
Beets, 2 plus
Brussel sprouts, 1 plus
Carrots, 2 plus
Turnip, 1 plus
All spices positive
Clam, 2 plus
Cocoa, 4 plus
Tea, 2 plus
Walnuts, 1 plus
Apples, 2 plus
Banana, 2 plus
Cherry, 1 plus
Grape, 4 plus
Pineapple 2 plus
Raisin, 1 plus
Strawberry, 1 plus

All positive reacting foods were eliminated from the diet

The pillows and mattress were covered with impervious coverings and house dust precautions were advised

She was advised to discard a camel hair coat she was wearing and hypo sensitization was started to dust, alternaria, hormodendron, and pollens of birch and tree of heaven Contact with silk and tobacco was avoided

Improvement occurred gradually and the abdominal symptoms with pain and diarrhea subsided. At the present writing this patient is work ing and more active than at any time during the past ten years A gain of 20 pounds in weight occurred and the nasal symptoms and asthmatic attacks have not recurred This case illustrates a complicated, multiple-sensitive, allergic individual whose history dates back since childhood The vomiting in childhood was probably due to the food factor and as she grew older additional food sensitivities and inhalant factors were superimposed At one time an abdominal operation was advised and none of the physicians she saw ever entertained the idea of an allergic basis for her symptoms

Chapter VI

Asthma

HISTORICAL

Asthma is the term used to describe a symptom complex characterized by recurrent attacks of dyspnea or breathlessness followed by wheezing respiration which is associated with marked prolongation of the expiratory phase and coughing The etiology is hypersensitivity The term bronchial asthma is a misnomer because asthma by definition is bronchial in origin There is an obstruction of the smaller bronchioles resulting from a constriction or narrowing of their lumina as a result of spasm of the bronchial muscles of swelling of the mucous membrane lining or of both factors

An English physician John Foyer published in 1698 *A Treatise of the Asthma* in which he described his own symptoms in a remarkably accurate manner stressing climatic conditions and dietetic indiscretions He divided asthma into two types one he designated continual asthma which was caused by some definite organic pathology the second type he called idiopathic and suggested as its cause the constriction of the bronchi and bladders of the lungs by windy spirits In 1784 Cullen attempted to classify spasmodic or convulsive asthma as a definite clinical entity due to constriction of the bronchial muscles

Hyde Salter in 1860 differentiated between spasmodic and cardiac asthma and he was the first to recognize its association with animal emanations and its hereditary tendency His book entitled

On Asthma Its Pathology and Treatment states that one of his asthmatic patients was obliged to take a sea voyage during the hay fever season Other patients troubled by association with rabbits horses cats, and dogs are mentioned Salter classified the causes of [illegible] *the bronchial tubes directly)* and [illegible] use *this* classification today

In 1872 Ernst von Leyden noted small [illegible] crystals in the *sputum* of asthmatic patients it was his *supposition that these* crystals acted as irritants to *the* mucous membrane of the bronchi

Heinrich Curschmann in 1882 observed spirals *in the* sputum and thought they were *the* cause of asthmatic attacks

It remained for W P Dunbar in 1905 to ascribe the cause of asthma to dusts of all kinds plant pollens and animal danders

Wolff Eisner in 1906 initiated the study of *pollen chemistry* by demonstrating that only certain types of pollen such as those of trees grasses and weeds cause hay *fever* and asthma

In 1910 Samuel J Meltzer by applying *horse dander to the* nose of a sensitive patient demonstrated *the* similarity between asthmatic attacks caused by pollen and those resulting from contact with *animal* emanations

Otto M Schloss in 1912 *demonstrated* that a food sensitivity to egg white in a child manifested itself as an asthma

These observations formed the foundation upon which modern workers have *built* a formidable mass of evidence linking asthma indisputably to the allergic state

FREQUENCY AND DISTRIBUTION

The incidence of asthma has been estimated variously from 05 per cent to 3 per cent of the population of the United States In about *one third* of all asthma patients *the* symptoms appeared originally during *the first* decade of life The incidence decreases rapidly after this so that it is quite low after *the* age of 60 G W Bray states that 25 *per cent of all* patients experienced symptoms during the first year of life

The United States Public Health Service in 1936 published the following *figures on chronic* diseases in *the* United States

Disease	*Number of Cases*
Rheumatism and arthritis	6 850 000
Heart disease	3 700 000
Hay fever and asthma	3 450 000
Chronic (asthmatic) bronchitis	1 700 000

These figures impress one with the high incidence of chronic respiratory disability since there were 5 150 000 individuals who had asthma or were potential asthmatic patients because of hay fever

In World War I 2 45 per 1000 young men were rejected by the draft boards because of asthma Among each 1000 veterans who received disability compensation fifteen years later 12 were found to have incurred asthma during military service

The statistics for World War II indicate that 4 4 per 1000 were rejected by selective service boards because of asthma One and seven tenths per 1000 were rejected for vasomotor rhinitis and 4 5 per 1000 for chronic rhinitis No statistics were available for hay fever but it is possible that seasonal hay fever is included in the figures for vasomotor and chronic rhinitis

Since the incidence of asthma is about the same in both sexes and since about one third of the cases begin in the first decade of life and another 50 per cent between the ages of 10 and 40 it can be predicted that the actual incidence of asthmatics in the United States is between 3 to 5 per cent of the entire population This estimate is higher than those of Warren T Vaughan (1939) 0 5 per cent Pipes 3 per cent and George Piness and Hyman Miller 0 5 per cent The fact that 40 to 50 per cent of seasonal and perennial hay fever patients eventually develop asthma is another important consideration in arriving at this high incidence

Sex

Males show a slight preponderance over females—53 to 54 per cent of all asthmatics Up to puberty there is a preponderance of males nearly three to one From puberty to menopause females *are slightly in the* majority—five to four After the age of 50 males again predominate five to four

Race and Economic Status

Asthma is more common in the white race, although an increasing frequency in young American Negroes has been noted since World War II Rich and poor alike are equally affected

PATHOLOGY

A general review of the anatomy of the bronchial tree will be given to better understand the pathologic findings in asthma Miller[1] and Macklin[2] demonstrate illustrations of the bronchi following the installation of lipiodol The trachea divides into two main bronchi at the carina, each about 15 millimeters in diameter These divide and subdivide to permeate the lung in a treelike fashion The lobule consists of a terminal bronchus leading into an atrium, which in turn connects with a number of air sacs These fine subdivisions carry on the major respiratory functions The branches of the pulmonary artery follow the bronchus to the center of the lobule The pulmonary veins start at the periphery of the lobule

The bronchial arteries branches of the thoracic aorta, likewise supply blood to the bronchi, bronchioles, lymphoid tissue and connective tissue, and to the pleura Ordinarily there is no anastomosis between these two blood supplies but a collateral circulation may be established in the presence of disease or infection The larger bronchi and rings of the trachea contain cartilage which gradually diminishes as division occurs

Some cartilage is present in bronchi having a diameter of 5 millimeters The very fine bronchi, smaller than 5 millimeters, are devoid of cartilage The smooth bronchial muscles are arranged in lattice like strands some of which go obliquely and some transversely Elastic fibers encircle the bronchi and are capable of stretching during inspiration by the force of inspired air and of becoming shortened and narrowed during expiration Bronchial mucous glands are found in the larger bronchi which secrete a mucus like substance

Death from asthma during an acute attack is relatively infrequent This is true only since the past ten years when it was repeatedly shown that most deaths during an attack of asthma resulted from the injudicious use of morphine Deaths from chronic asthma and

emphysema are, however, more frequent than the literature would imply

Four deaths from chronic asthma occurred on my service at the Cook County Hospital during the past two years immediately following the intravenous use of aminophyllin Ventricular fibrillation resulting from the too rapid injection of the drug was suspected as the immediate cause of death although a drug sensitivity could not be ruled out

Autopsy Findings

On gross examination emphysema with distention of the lungs is characteristic At times the distention is so marked that ridges are present on the surface of the lungs from the pressure against the bony structures The lungs have a doughy, elastic feeling because of the scattered areas of emphysema and atelectasis present throughout

The cut section reveals excess mucus in the lumen of the bronchi and plugs of thick tenacious mucus with fibrin may be seen Dilatation of the smaller bronchioles and alveoli may be seen Microscopically, a cellular infiltration consisting of eosinophils, plasma cells, and lymphocytes of the mucosa, submucosa, and mucous glands are present The bronchial musculature shows hypertrophy and increasing thickness of the bronchial wall with narrowing of the lumen Degenerative mucous glands are frequently observed The bronchi and smaller bronchioles contain secretion which may be thin and mucoid in character or sticky tenacious mucous plugs which entirely block their opening The lining mucosa is hyperemic or pale and edematous and thrown into folds, thus aiding in complete obstruction of the bronchi

Areas of atelectasis of the lung are usually associated with complete obstruction by mucous plugs of smaller bronchi

The early changes in asthma may not be so pronounced and the findings are completely reversible as symptoms subside When asthma continues and becomes more chronic the findings tend to become irreversible with definite thickening of the bronchial muscles, narrowed lumen, and emphysematous changes Emphysema with its associated tissue changes is a sequel to asthma and not a

complication It definitely is present in every attack but when it occurs early it is entirely reversible

Subcutaneous emphysema is a rather rare complication of asthma and may occur in children There have been some 12 cases reported in the literature up to the present time

Lamson and Butt (1937) reviewed the literature on deaths in asthma and included an autopsy study of 48 cases where death was attributed to this condition Their findings show that asthma did not predispose to cardiac disease

Alexander likewise noted that during the asthmatic attack the heart frequently appears fluoroscopically smaller than normal I have noted this finding frequently while fluoroscoping the patient during an acute attack of asthma

This finding may be explained by diminished cardiac filling which occurs with bronchospasm and due to diminished intrathoracic negative pressure Therefore with a smaller amount of blood volume in the cardiac chambers during an asthmatic attack, the heart actually may be spared Damage to the myocardium, however, may occur from prolonged anoxia

Unger has demonstrated right ventricular hypertrophy in chronic asthma, although no evidence of failure was present

In experimental anaphylaxis in guinea pigs, Criep found cardiac manifestations of arrhythmias and auricular or ventricular asystole followed by cardiac standstill This phenomenon may be observed in early asphyxiation and is not characteristic of anaphylaxis

ETIOLOGY

There are several factors which influence the onset of asthmatic symptoms in any individual The most important factor is heredity

The Constitutional Factor, or Heredity

Where both parents are allergic, the offspring tend to develop asthma at an early age It has likewise been noted that the children of asthmatic parents tend to develop asthma rather than other types of allergy, and that they may even be sensitive to the same allergens The exact mechanism of inheritance is not known at present but it seems that certain individuals have a constitutional predisposition

to develop asthma under various environmental conditions with exposure to allergens

Certain allergic conditions such as hay fever perennial allergic rhinitis and atopic dermatitis predispose to asthma A detailed his tory will frequently disclose sneezing and nasal stuffiness preceding the onset of asthmatic symptoms Often patients state they have fre quent colds when in reality the colds are symptoms of allergic rhinitis It is obvious that prolonged attacks of allergic rhinitis weaken the defensive powers of the upper respiratory mucosa and asthma follows when the initial first line of defense is broken

The Effect of Endocrines

Disturbances of various glands of internal secretion have been suspected as causative factors in allergic conditions The relief af forded by epinephrine might suggest some suprarenal deficiency Likewise the often associated hypotension and hypoglycemia point to some disturbance of this gland There has never been any demon stration that allergic conditions are associated with organic changes in the adrenal glands

Disturbances of the pancreas as seen in true diabetes are rarely associated with allergic states

The thymus gland at one time was thought to have an etiologic influence in asthma Thymic deaths occurring in infants are thought by George Waldbott to be due to allergy Some may be true cases of bronchial asthma affecting an infant who also shows an enlarged thymus gland

During pregnancy many patients become free of asthmatic and hay fever symptoms however after delivery these symptoms usually return Some disturbance in the reproductive glands such as the ovaries and of the pituitary and thyroid has been suspected as a result of the studies of Zondek and Bromberg They believe that an actual endocrine allergy exists whereby the endocrine glands may react to their own hormones which are thus altered in some way Positive skin reactions to hormones with specific circulating reagins have been demonstrated by Zondek and Bromberg and desensitiza tion to the pituitary hormone has been helpful in their experience This work is as yet (1951) not confirmed and one can only conclude

at present that these hormones affect the sympathetic nervous system in an already predisposed allergic individual

Disturbances of Metabolism and Biochemical Alteration

Various disturbances in calcium, phosphorus, ascorbic acid, blood chlorides, and hypoglycemia have been reported from time to time by different observers

Calcium and ascorbic acid have been used empirically in allergic conditions, but it has never actually been proved that these sub stances are etiologically related to the allergic state Neither has their use resulted in relief of allergic symptoms

Nervous and Psychic Influences

Psychosomatic influences have recently been thought to be etio logic factors in asthma, however, they are rarely responsible for an asthmatic attack except in an already allergic individual It is true that these patients, especially children, have a fear of suffocation, and an impending asthmatic seizure may aggravate the condition and even occasionally incite an attack, yet the underlying cause is the allergic state or capacity to develop reagins Psychoneurosis may ac company the allergic state as it does other prolonged illnesses, and may aggravate the condition, but it need not be the basic cause

RESPIRATORY PHYSIOLOGY

Pulmonary function may be divided into two phases The first may be called the ventilatory phase and consists of an alternating flow of air in and out of the lungs This may be thought of as a bellows like action and depends upon the muscles employed in pul monary ventilation, the bony framework of the chest, patent air passageways, intact nerve pathways and normal elasticity and struc- ture of the pleura mediastinal contents, and lungs The second phase of pulmonary fun[illegible] exchange phase and con sists of an exch[illegible] between the pul monary alveoli [illegible] ilatory phase of pulmonary function is of chief concern since this component is chiefly impaired in asthma

To measure the functional reserve of any organ in the body, two essential things must be known First, the rate at which the specific

function is carried out, and second, the maximum rate at which the specific function can be carried out If these two things can be measured, an accurate idea can be obtained concerning the functional status of the organ

The importance of measuring the functional reserve of an organ is immediately evident Long before there are clinical signs of pathology in an organ or organ system, the capacity of an organ to carry on its normal activities may be considerably reduced Similarly, there may be pathology elsewhere in the body, which is compensated for by increased activity of an organ or organs In this instance, also the functional reserve of the organ is decreased

One organ system which is ideally suited for these tests, but which has been rarely used, is the respiratory system In the past, the vital capacity was used as an estimate of the function of the respiratory system However, this merely shows the volume of the lungs that is available for respiration and there is no time element involved Recently, a satisfactory method has been devised for the measurement of the functional reserve of the respiratory system This measurement has been called the resting ventilatory reserve or breathing reserve

The maximum voluntary ventilatory capacity and the minute volume determine the breathing reserve Both of these can be easily measured When measuring the voluntary ventilatory capacity, the patient breathes in and out as hard as he can for a period of time (usually twenty to thirty seconds) A spirometer with a special attachment is used for this test and the result is expressed in liters per minutes This has been called dynamic spirometry

The breathing reserve is calculated as follows when *M V V C* is maximum voluntary ventilatory capacity, *M V* is minute volume, and *B.R* is breathing reserve

$$\frac{M\,V\,V\,C - M\,V}{M\,V\,V\,C} \times 100 = B.R$$

The normal breathing reserve ranges between 96 and 98 per cent

The breathing reserve enables one to measure accurately the functional reserve of the respiratory system and to use objective methods for studying the beneficial effects of different types of therapy on

pulmonary pathology This is particularly useful in the study of asthma, since it has been shown that the vital capacity does not adequately measure the pulmonary insufficiency

SYMPTOMS AND SIGNS

The acute stage of asthma is characterized by paroxysms with a tendency for periodic recurrence at different intervals Between attacks no symptoms or physical findings can be ascertained The chronic stage is preceded by increasingly shorter intervals between attacks, until continuous asthma is present

Dyspnea and wheezing are the characteristic symptoms, usually coming on suddenly without warning The patient is awakened by a sense of suffocation and there is extreme difficulty in breathing The respirations are slow and labored, and it becomes difficult to get air into the lungs during inspiration, the greatest difficulty occurs in expelling the air during expiration This is caused by edema in the bronchioles and constriction of the lumina The accessory muscles of respiration are called upon to attempt to force the air out of the lungs, this results in a prolongation of the expiratory phase and the characteristic wheeze which may be heard at some distance from the patient As the attack continues, the dyspnea increases and an anxious expression appears on the facies The forehead is covered with beads of cold perspiration, and the pulse is small and rapid A dusky pallor may be visible on the skin while the lips assume a cyanotic color The fingers and toes become cyanotic During the initial attack, the patient may fear suffocation or impending death and often suffers actual panic In such a state, the physician may find it difficult to relieve the attack with the usual measures and it becomes of great importance to reassure the patient A paroxysm of coughing is often followed by expectoration of retained secretions, and breathing then becomes easier The dyspnea and wheezing disappear entirely within a short time, leaving the patient in an exhausted and weak condition A restful sleep usually follows

Although the patient has marked difficulty in both the inspiratory and expiratory phases of respiration, the expiratory phase is attended with greater distress

The symptoms may resemble those of a state of shock, with cold,

clammy perspiration subnormal temperature and a rapid thready pulse indeed the patient is suffering from allergic shock

In children quite commonly an attack of asthma is ushered in by a high temperature and very often pneumonia is suspected or wrongly diagnosed

Physical Findings

On inspection the patient is observed to be breathing with difficulty using the accessory muscles of respiration with a corresponding widening and fixing of the intercostal spaces with the ribs in horizontal position as is seen in deep inspiration

On percussion a hyperresonance throughout more marked over the bases of the lung can be elicited

On auscultation numerous wheezing sibilant and sonorous rales are heard throughout the chest with the expiratory phase definitely prolonged over the inspiratory phase It should be borne in mind that an asthmatic may be in acute distress without prominent wheezing or rales and that one may often detect fine rales by placing the diaphragm at the patient s open mouth and having him breathe at it

Laboratory Findings

The blood characteristically shows an increase in eosinophils which may range from 5 to 50 per cent of the differential count This is one of the most common findings in asthma patients Early in the attack there may be very little sputum but at the termination of the asthmatic attack expectoration of mucous plugs which contain Charcot Leyden crystals and eosinophils usually occurs The urine shows no abnormal findings in uncomplicated cases the blood chemistry reveals normal values including the calcium content in which I have never seen a discrepancy Electrocardiography usually shows no variations from the normal between attacks During an attack of asthma there are variations from the normal which are difficult to interpret these usually revert to normal when the attack is over In the acute attack electrocardiography may reveal changes characteristic of acute coronary insufficiency For accurate evaluation it is therefore advisable to run electrocardiograms after rather than during an acute attack

X ray Findings

Films of the chest do not reveal any abnormal findings in the uncomplicated asthmatic however chest plates of chronic asthmatics may show evidence of heavy hilar shadows bronchiectasis emphysema or a combination of these The fluoroscopic findings during an asthmatic attack are an emphysema with depressed diaphragmatic arches The heart is of normal or diminished size

PHYSIOLOGY

Asthma is produced by a constriction of the bronchioles throughout the entire lung parenchyma caused by a spasm of the fine circular smooth muscle of the bronchiole or by an edema of the mucous lining of the bronchiole or by a combination of both factors The antigen usually gains access to the lung via the blood stream

The bronchiolar musculature is under the control of the autonomic nervous system of which the sympathetic or thoracolumbar division serves as the *dilator* supply and is indeed the dominating influence normally over the *constrictor* parasympathetic or craniosacral division of the autonomic system In man one of the responses of the body to an antigen is the constriction of the bronchiolar musculature of the lung leading to diminished air supply to the alveoli and to a relatively inelastic indistensible lung This situation of course results in a marked lowering of the vital capacity of the dyspneic point and the patient is in much the same distress as a person suffering from cardiac insufficiency Indeed the mechanism by which the dyspnea is produced is comparable in that it is the vagal reflexes inaugurated by this inelastic lung which affect the respiratory center so as to produce tachypnea and dyspnea Experimentally as W T Harrison has shown sectioning of the vagi in an inelastic lung markedly decreases or abolishes the dyspnea In order to reverse the sequence of events just described we resort to the use of a powerful sympathomimetic drug epinephrine whose action in stimulating the sympathetics results in a dilatation of the bronchioles and a vasoconstriction of the blood supply to the bronchial mucosa these actions accomplishing a free access of air and a diminished secretion of mucous plugs By so returning the lung to its normal elasticity the vital capacity returns to normal and the dyspnea is abolished

PATHOLOGY

Many pathologists performing autopsies on patients who have died in acute attacks of asthma have regularly found a narrowing of the lumina of the smaller bronchi and bronchioles caused by the following (1) A hypertrophy of the fine circular muscles and an increase in the thickness of their walls, the many mucous glands which lubricate the bronchi also become enlarged and secrete much more mucus than normally, and (2) an edema of the mucous membrane lining the bronchi

The microscopic anatomy reveals eosinophilic infiltration and an increase in mononuclear cells Charcot Leyden crystals and Curschmann s spirals are usually found in the mucosa and in expectorated sputum

Varying degrees of emphysema and bronchiectasis may be seen in chronic cases

DIAGNOSIS

The diagnosis of asthma is made from the clinical symptoms which characterize the disorder, together with the physical findings and the demonstration of the criteria of allergy (such as positive skin tests) and other confirmatory laboratory evidence

DIFFERENTIAL DIAGNOSIS

In adults asthma must be differentiated from such conditions as paroxysmal nocturnal dyspnea of cardiac disease, mediastinal tumor, pulmonary tuberculosis pressure in the chest from aneurysm or foreign body bronchogenic carcinoma of the lung and metastatic carcinoma of the lung chronic bronchitis chronic emphysema, cor pulmonale chronic glomerulonephritis, and substernal thyroid

Paroxysmal Nocturnal Dyspnea, or Cardiac Asthma

Cardiac asthma may be confused with asthma when asthma occurs in individuals who are in the age group in which degenerative heart disease is common The differential diagnosis is important because the difference in treatment is so pronounced Dyspnea of cardiac disease is due in most cases to left ventricular failure and is caused by marked passive congestion of the lung Attacks usually occur at night

after the patient has been asleep for some time He is suddenly awakened by a feeling of choking, gasping, and intense inspiratory dyspnea, these attacks may be brought on by reflex stimulation of the respiratory center, as by coughing, a desire to urinate, a warm room, or sudden awakening following a disturbing dream Sitting upright in bed lessens the dyspnea by increasing the pulmonary ventilation On examination, the patient may be found to have a hypertension, with enlargement of the heart and other evidences of chronic heart disease or luetic aortic disease The physical examination may reveal wheezing, sibilant, and sonorous râles similar to those found in asthma

It must be remembered that the middle aged patient may have both asthma and some degree of heart disease, which latter factor may precipitate dyspnea by the following mechanism the pulmonary congestion incident to left ventricular failure will produce bronchoconstriction and wheezing by acting as a nonspecific irritant to which the lung responds as it once did to an antigen This sequence thus constitutes a conditioned reflex

Of great help in differential diagnosis is a history of preceding or associated hay fever or rhinitis a sensitivity to some food, a family history of allergy, a history of manifestation of allergy in childhood, recurring colds or bronchitis, urticaria, migraine, eczema, or cyclic vomiting

Another point of differentiation is that asthma most often occurs in younger individuals

In asthma, the blood pressure is usually low, and the venous pressure is normal or subnormal, indeed, this constitutes a valuable aid in the differential diagnosis, because cardiac patients so commonly have increased venous pressure The presence of positive skin tests, plus blood eosinophilia tilts the balance toward a diagnosis of asthma

Mediastinal Tumor

Mediastinal tumor produces dyspnea by pressure on or displacement of the trachea The findings are increased dullness over the upper portion of the sternum, plus fluoroscopic and roentgen visualization of an increased density over this same upper portion

Pulmonary Tuberculosis

Patients suffering from pulmonary tuberculosis may also have asthma on an allergic basis due either to the ordinary sensitivities or to the development of a sensitivity to the products of the tubercle bacillus Careful physical examination may reveal fine moist râles over one or both apices and infraclavicular areas Fluoroscopy and x ray usually demonstrate destruction of lung tissue in the apices or infraclavicular areas The presence of afternoon fever, persistent rapid pulse, and other characteristic toxic symptoms helps in the diagnosis, and the finding of tubercle bacilli in the sputum confirms it

Aortic Aneurysm

The finding of a widened aorta, with expansile pulsation and the presence of a bruit over the second intercostal space to right or left of the sternum in an individual with positive serology, plus fluoroscopic findings of a pulsating mass synchronous with the pulsations of the aorta, spell aneurysm

Foreign Body

A foreign body in a bronchus, occurring especially in children, may present unusual difficulty in diagnosis The important findings are unilateral wheezing and congestion of one side of the chest Bronchoscopic and x ray visualization will usually localize the foreign body

Primary Bronchogenic Carcinoma of the Lung

The first manifestation of a primary bronchogenic carcinoma of the lung may be wheezing and cough occurring in a patient of middle age Usually there will be an accompanying expectoration of blood tinged sputum and physical findings of impaired resonance to dullness over an upper lobe with suppressed breath sounds These findings are compatible with those of atelectasis Fluoroscopic and x ray examination demonstrate infiltration in an area of lung surrounding a bronchus Lipiodol instillation in the bronchial tree plus bronchoscopy will usually show the carcinomatous infiltration

Metastatic Carcinoma of the Lung

Diagnosis here is made on the history and the x ray findings of cannon ball distribution of infiltration throughout both lungs

Chronic Bronchitis

A history of repeated upper respiratory infections with cough and expectoration of purulent material plus findings of coarse moist râles along the larger bronchi is suggestive of chronic bronchitis

Chronic Emphysema (With or Without Cor Pulmonale)

Important here is a history of a strenuous occupation such as athletics lifting or other physical exertion (like that of musicians playing wind instruments) Chronic asthma itself may lead to emphysema If the emphysema is severe enough a cor pulmonale with right heart failure may be expected and may be diagnosed by the presence of cyanosis increased venous pressure and enlargement of the right heart, in addition to the sibilant and sonorous râles heard on auscultation and the barrel chest seen on inspection X ray examination confirms the diagnosis

Chronic Glomerulonephritis

This condition may simulate asthma in two ways first by the production of hypertensive heart disease with cardiac dyspnea and second, by the hyperpnea present in the acidosis of the pre uremic or uremic state This diagnosis can usually be made without difficulty on the basis of the blood pressure, urine findings and blood chemistry

Substernal Thyroid

A substernal thyroid enlargement often gives rise to sensations of choking gasping and wheezing This condition can be diagnosed by fluoroscopic and x ray findings of widening at the upper end of the mediastinum (constituting a type of mediastinal tumor) Basal metabolic rate determinations and blood chemistry may aid in the diagnosis if the thyroid is hyperactive

Enlarged Tracheobronchial Lymph Nodes and Enlarged Thymus in Children

These conditions should be remembered in considering dyspnea in children and can be ruled out by fluoroscopic and x ray examination

Chapter VII

The Etiologic Diagnosis and Treatment of Asthma

There are three major categories of asthmatic patients One group comprises patients who have the frankly allergic type of asthma, and in whom positive skin tests and eosinophilia in the sputum and blood can be demonstrated The second group consists of patients, usually past 50 although not necessarily, who give no family history of allergy, in whom skin tests are negative, and in whom the asthma is preceded by frequent attacks of upper respiratory infections perennial rhinitis or an attack of pneumonia The third group comprises those patients in whom there is an element of the previous types, with various degrees of dominance of one or the other

GROUP I THE FRANKLY ALLERGIC TYPE

This group comprises the large majority, probably 75 per cent of the total number of asthmatic patients

If one will pay particular attention to the history, one can elicit some allergic disturbance occurring in the patient, perhaps years before, such as a seasonal rhinitis that had occurred for years but which was so slight that no significance was attached to it—the patient believing that these attacks were merely attacks of acute coryza Also, attacks of perennial rhinitis would occur for years under the guise of 'colds" Sometimes urticaria or a food intolerance disturbed the patient years before, and only after a carefully scrutinized history may these significant findings be uncovered and correctly interpreted in the light of the present asthmatic symptoms The

etiologic agent in most instances can be found in the inhalant groups, such as chicken feathers, goose and duck feathers, dog, cat, or bird hair, orris root, pyrethrum, horse dander, cottonseed, linseed, silk, wool, rabbit hair, house dust, glue, goat hair, kapok, mattress dust, molds, and yeasts in the air and house, and various pollens Foods commonly eaten may also play a role, in addition to those substances already mentioned. Foods by inhalation, such as may occur among bakers, millers, and housewives, are also common causes Farmers exposed to grain dust and smuts also may be affected with a severe type of asthma following inhalation of these fungi Corn, rye, and barley dust may be responsible for a severe type of asthma As an example of the frankly allergic type developing in an individual past 50, the author cites the following case from his practice A druggist at the age of 50 became sensitized to lycopodium dust spores which are used in drying pills and capsules Skin tests to powdered lycopodium were positive and the complete elimination of lycopodium from his environment resulted in a complete cure of his symptoms In testing these patients, it is very important to do not only cutaneous or scratch tests but also intradermal tests, and even passive transfer tests must be resorted to in many cases in order to determine the causative factor All of these tests, including passive transfer, must be negative before one classifies the patient in group II

Environmental control of these patients is essential to relieve their asthma Rubberized pillow and mattress covers, as well as complete house dust precautions should be insisted upon Other inhalant factors determined by skin test to be etiologically significant, must be avoided entirely This statement sounds simple enough, yet in practice it is a very difficult procedure to enforce unless patients are carefully informed on how to avoid inhalant substances in the various forms to which they are exposed unknowingly Visits to the home by the physician are often necessary to point out unwitting errors and oversights in this regard For example, a patient who reacted strongly to rabbit hair and horse hair obtained relief only after removing an animal hair padding under the carpeting which she had completely overlooked It was difficult to convince this patient, in spite of the fact that upon a short stay in the hospital, on several occasions, the symptoms would clear up in a few days only to recur when the patient returned home

It is also important to hyposensitize these patients, especially those

sensitive to house dust, orris root, silk, molds yeast, and pollen It is virtually impossible to escape these inhalant substances either in the home or outdoors (see discussion of hyposensitization in chapter VI)

Patients should also be retested from time to time, particularly if asthmatic symptoms recur after a period of relief However, it is rare for relapses to occur after environmental factors have been completely controlled and hyposensitization treatments given correctly

GROUP II NO HISTORY OF ALLERGY OBTAINABLE NEGATIVE SKIN TESTS

In this group of patients changes in environment, diet, and weather have no influence on their asthma The asthma is usually severe and may be even rapidly fatal Pathologically, there seems to be more secretion in the bronchi and less spasm than in the frankly allergic group There may also be infection in the paranasal sinuses and bronchi and complications of bronchiectasis and emphysema seem to follow early There are many theories at the present time as to the etiology of asthma in these patients, perhaps the most plausible one is the hypothesis that an allergy results from products of infection

The first step in the treatment of these patients is to make sure that they belong in group II—that skin tests and passive transfer tests are negative Then the control of the sinusitis and nasal infections by proper local and systemic means is in order Control of upper respiratory infections in general is essential Sometimes the procedure of bronchoscopy, which eliminates the excess secretions and pus, may give these patients some relief Potassium iodide 10 to 15 gr three times a day, often helps to liquefy secretions and aids in expectoration, as does ammonium chloride, 15 gr four times a day The following prescription has been found very useful in this type of asthma

℞ Spirits chloroform	5 minims
Apomorphine hydrochloride,	1 gr
Potassium iodide	4 drachms
Tincture of Lobelia	4 drachms
Syrup of Sarsaparilla to make	4 fluid ounces

Directions 1 teaspoonful well diluted with water, every 4 hours

Aminopylline gr 7½ in 10 cc of normal saline given intravenously is often beneficial in this group

Epinephrine 1 500 in oil 1 cc intramuscularly may control the wheezing for as long as twenty four to forty eight hours but may be given every four to six hours if necessary (Note the ampul should be immersed in warm water and shaken vigorously before opening and using so as to get the particles of epinephrine in smooth suspension)

Aminophylline suppositories gr 5 may give overnight relief and supplement intravenous aminophylline and epinephrine

There is some evidence that x ray therapy over the chest combined with ultraviolet irradiation may be of some benefit in a few selected cases The author has not had much success with this form of therapy

From the author s personal experience with a series of patients the use of iodized oil in the bronchial tree is rather disappointing Its use was of no benefit in 85 per cent of the patients in our series About 15 per cent of the patients were temporarily improved but as soon as the instillations of iodized oil were discontinued the asthma recurred The real danger is that the oil will remain in the lungs for from one to three years and may be a potential source of a lipoid pneumonia atelectasis or a possible lung abscess

For the distressing cough Hycodan bitartrate 5 mg tablets may give considerable relief if given every three or four hours This product is a derivative of codein yet has none of the undesirable properties of codein and is not habit forming

The use of morphine pantopon and demerol hydrochloride is to be condemned in asthma since they are habit forming and so depress the cough reflex center that the patient is not able to bring up the mucous plugs and tenacious sputum necessary for relief and may virtually drown in his own secretions

In status asthmaticus the judicious use of epinephrine plain and in oil ether in oil per rectum and sedation has often failed One may give a subcutaneous injection of 35 mg demerol hydrochloride together with 0 5 cc of a 1 1000 aqueous epinephrine solution for one dose This combination often brings the attack under control when other measures have failed Demerol chemically is ethyl 1 methyl 4 phenylpiperidine 4 carboxylate

The spasmolytic action of this drug is in part due to depression of the parasympathetic endings but it is primarily the result of a

direct papaverine like depression of the muscle fibers Its action lies between that of morphine and codein and since it is a habit forming drug its use in chronic asthma is limited Aqueous epinephrine 1 1000 subcutaneously 3 to 5 minims given at twenty to thirty minute intervals may control marked wheezing It is not advisable to give 1 cc doses since bronchial relaxation usually follows the smaller amounts without the added toxic effects of large doses of epinephrine such as marked pallor rapid pulse and syncope Epinephrine 1 1000 solution used in a vaporizer and inhaled deeply three or four times can be used several times a day usually with symptomatic relief

Helium and oxygen as originally advised by Barach are used in severe paroxysms of asthma and administered through the Boothby Lovelace Bulbulian (B L B) mask which fits over the nose leaving the mouth open enough for eating talking and drinking The gas mixture consists of 20 per cent oxygen and 80 per cent helium and its beneficial effects depend on its low specific gravity as compared with that of oxygen Tanks of helium oxygen and of pure oxygen are connected to the mask by Y valves and as the patient improves more oxygen and less helium are used

Great caution should be exercised in using drugs in asthma since many patients are sensitive to drug compounds such as aspirin phenobarbital pentobarbital codein and morphine Unfortunately these complex chemicals do not give reactions by skin tests and the only way to determine sensitivity to them is to use them—but the trial has not always been safe or easy It is far safer to use those drugs having simpler chemical formulas such as bromides chloral hydrate and paraldehyde Five per cent glucose in normal saline solution 1000 cc intravenously may be extremely helpful in patients who are dehydrated and as much as 2000 cc can be safely given in a twenty four hour period

Ether and olive oil a mixture of equal parts 150 cc to 200 cc given per rectum every six to eight hours if needed often aids materially in shortening the course of a severe asthmatic attack

The efficacy of vaccine therapy remains a controversial issue Some workers claim good results with autogenous vaccines and others claim equally good results with stock vaccines The author s opinion of vaccines in this type of asthma is that of a nonspecific effect similar to the results obtained with any foreign protein injection such as

proteolac, milk protein, or typhoid vaccine If the vaccine produces a local reaction at the site of injection, improvement of the symptoms may occur temporarily, only to recur again The use of vaccines in general has been very disappointing Small, continued doses of ACTH or cortisone, carefully administered, may alleviate the asthmatic paroxysms

GROUP III EARLY ALLERGIC HISTORY LATER INFECTION

The third group of asthma patients comprises those who originally began as frankly allergic patients and who, perhaps years later, developed infections in the bronchial tree and paranasal sinuses It is important to test these patients thoroughly and to make an attempt to eliminate all inhalant as well as food allergens which had originally caused the asthmatic symptoms The treatment of the sinuses and bacterial infection in the bronchi resolves itself into conservative local measures to aid drainage and general measures aimed at increasing the general body resistance The use of iron, arsenic in small doses, such as Fowler s solution 3 to 5 minims and vitamins may be beneficial if indicated Radical nasal surgery has done more harm than good, whereas conservative local measures plus adequate control of the allergic background offers the greatest hope for relief in these patients

Case Reports

Mrs L P, age 24, was seen because of asthma which had begun two years before during her sixth month of pregnancy and had persisted since There was a history of sneezing and rhinorrhea throughout the year for several years and a history of her father having chronic asthma Examination disclosed sibilant and sonorous rales over both lungs and nasal examination revealed hypertrophied boggy inferior turbinates Eosinophils in the blood were 9 per cent, with a normal total leukocyte count Intradermal skin tests were strongly positive to feathers, dust, mattress dust, wool, and animal hair Smaller reactions were obtained to chocolate and milk

Instructions were given to cover the pillows and mattress with non allergic covers, and chocolate and milk were excluded from the diet Hyposensitization was given to an autogenous house dust extract This patient rapidly improved and three years later, has not experienced an asthmatic or rhinitis attack since

The interesting feature of this patient is that she was an allergic individual for years before her pregnancy During the last three months of her pregnancy she literally forced herself to drink more milk than she had been accustomed to, in spite of a dislike for it This procedure, plus the added strain of pregnancy, upset the allergic balance and the summation effect of the exposure to several antigens combined to produce a severe asthma which persisted until the removal of these antigens

It is of utmost importance that pregnant women who are allergic should not partake of unusual amounts of any particular food, especially where there is a dislike for the food, since they may be potentially sensitive to the food but may show only slight or no symptoms on small quantities Vaughan has termed this 'balanced allergic state' and a summation of several antigens, plus the added strain during the latter part of pregnancy, may upset this balance with the production of symptoms

J L, boy, age 10, came in because of hay fever from August 15 to September 15 and asthma throughout the year The hay fever symptoms had been present for four years and the asthma had begun two years before There were also periodic attacks of urticaria which occurred during the previous four years In the family history, the father had a perennial rhinitis and a contact dermatitis on the hands caused by handling parsnips The paternal uncle had hay fever Examination disclosed wheezing and sibilant and sonorous râles over both lungs Previous pollen injections for hay fever and one year of treatment with oral pollen preparations had given no relief

On complete testing, it was found that large reactions were obtained to ragweed (giant and short) corn, cantaloupe, and shrimp, and smaller reactions to cottonwood tree pollen, cat hair, chocolate, and tomato A cat was ordered removed from the house and treatment was given to the ragweeds and cotton wood Under this regime, improvement was rapid and the hay fever was well under control

Mr A L, age 32, had had asthma for three years He also had had a dog in the house for the same length of time Tests revealed a large reaction only to dog dander An attempt was made to hyposensitize him to dog dander since he was not willing to dispose of the dog Asthma persisted, however, and he was not relieved until the dog was disposed of and the house thoroughly cleaned of dog hair The asthma stopped completely when this was done This again emphasizes that complete

elimination of the offending allergen must be insisted upon before relief can be expected

Mrs M S, age 31, gave a history of a chronic neurodermatitis, lasting fifteen years, which affected chiefly the face, back of the neck, bends of the elbows and behind the knees It would improve in summer, only to recur in the fall and winter months Hay fever had been present for four years and asthma had begun two years previously Her father and one cousin had asthma

Tests showed large reactions to silk, grasses, ragweed (giant and short), and yeast Smaller reactions were present to orange and cabbage Silk clothing and undergarments were removed from contact with the patient and orange, cabbage, and foods containing yeast were omitted from the diet Treatment was given to grasses and ragweeds The neurodermatitis, with lichenification and itching of the skin, cleared up upon the removal of silk clothing Asthma and hay fever symptoms were controlled after treatment was instituted to the grass and ragweed pollen and to a silk extract.

Subsequently, this patient was married and treatments had to be discontinued because she lived near an army camp where her husband was stationed. She returned to Chicago some months later because of pregnancy She had no further symptoms until the delivery of the baby Within one hour after delivery, however, she began to have severe asthma This is not unusual as many allergic women who have had no symptoms during pregnancy will suffer a recurrence of symptoms after the birth of the baby

Mrs G F, age 25, wife of a physician, complained of a perennial rhinitis of three or four years duration accompanied by sneezing, itching of the nose, and a clear watery nasal discharge She had been treated by several otolarygologists, and on two occasions the antra were punctured About three weeks following the last antral puncture cough and asthma developed and wheezing would occur three to four times during the week In the history, one uncle had hay fever There was an additional history of a chronic colitis for many years and someone suspected a gastric ulcer, although x ray examination of the gastrointestinal tract was negative for ulcer

Examination revealed a pale, undernourished female, with considerable cough and wheezing bilaterally over both lungs The blood eosinophilia was 16 per cent

Tests were strongly positive to all feathers and egg white, beets, and banana

This patient was working as a social service worker in a sanitarium and she was in contact with chickens and ducks, which were kept in the yard Elimination of contact to feathers and avoidance of eggs, beets and banana in the diet stopped the asthma

This patient rapidly gained weight and the gastric and colon symptoms promptly cleared up The patient s husband, who is a physician, informed me some three years later that he was the proud father of a baby son, and that no further rhinitis asthma or colitis symptoms had appeared

This case illustrates an allergic response to inhalants and foods beginning with perennial rhinitis, then an allergic manifestation of the gastrointestinal tract Following surgery to the nose, asthma followed These manifestations cleared up when contact to these allergens was interrupted

Many cases of asthma can be cited that are caused by inhalant factors and are not relieved until contact with these substances is broken completely The author knows of one patient, a bird fancier, who was sensitive to canary and parrot feathers He simply had to seek another occupation Others sensitive to dogs and cats are frequently seen House dust, wool, silk, orris root, pyrethrum dust, and dust from deterioration of cotton linters in old mattresses are also commonly observed

In younger adults and children, foods such as wheat eggs, milk and the cereals are more common antigens causing asthma A more detailed list giving the identity of some common inhalant substances causing allergic symptoms will be found in the Appendix

RELATION OF ASTHMA TO MILITARY SERVICE

Asthma occurring in young men of military age is usually the allergic type A large percentage of this group also have an associated hay fever, and it is difficult while in military service to avoid contact with the various hay fever flora and other inhalant and food allergens to which they are sensitive From my personal observations of these patients during the last war, those who were taken for military service spent more days in military hospitals, because of severe hay fever and asthma, than in military regime Many had to be returned and discharged from the service

I would consider young men suffering from severe hay fever as unfit for military service Those with mild hay fever symptoms

however, which required little or no treatment in civilian life, could be used for limited duty, with periodic observation of symptoms

Asthma is a serious disease at any age and requires constant observation and treatment Under adverse conditions, such as prolonged strain and exposure to wet and cold severe asthma may ensue The safest procedure is not to allow anyone in the armed forces with asthma, since they sooner or later become a burden and overcrowd military hospitals that are needed for acute diseases and the emergencies that occur.

STATUS ASTHMATICUS

This special group of intractable asthmatics can be considered as a subdivision of group II where infections in the paranasal sinuses and bronchial tubes are present and skin tests to inhalants and foods are negative Most deaths from asthma are due to status asthmaticus It usually occurs between the ages of 40 and 60 and approximately 40 per cent have the disease for less than five years 60 per cent for less than two years There is a period of very intense dyspnea, marked wheezing, and an associated outpouring of an extremely tenacious viscid secretion which produces an inelastic, relatively indistensible lung and diminishes the vital capacity Massive pulmonary collapse following complete bronchial obstruction has been described This intractable asthmatic condition may be prolonged to several days or a week, when it terminates with an abundant expectoration Death may occur from exhaustion or heart failure Fever of 101° F to 102° F may be present on the third day and may continue for four or five days or until the attack is over Pulmonary consolidation with physical signs of pneumonia may complicate the picture When intractable status asthmaticus occurs the patient no longer responds to epinephrine and becomes epinephrine fast Any measures that will terminate the continuous attack even temporarily will stop the mechanism responsible for the persistent symptoms The patient will then again respond to epinephrine or other drugs that relieve asthma One of the best measures to use in this condition is the inhalation of oxygen 20 per cent and helium 80 per cent by means of the B L B mask The low specific gravity of this gas allows it to penetrate through the obstructed bronchioles Epinephrine, if already given previously without effect, should be discontinued Helium and oxygen should be inhaled for as long a period as three

or four hours at one time, if necessary, and may be continued for a longer period if relief does not ensue Periodic inhalations lasting one to two hours may be necessary for a period of two to five days to relieve a severe attack Once the attack is brought under control, epinephrine in oil 1 500 intramuscularly may be given for the mild wheezing which may recur Complete anesthesia with the use of ether has been tried with success in breaking up a severe attack of intractable asthma A mixture of equal parts of ether in oil, 150 to 200 cc, as a retention enema will often stop the attack

Sedation may be of use in terminating the attack and may be achieved by chloral hydrate, phenobarbital gr 1½ or nembutal gr 3 dilaudid gr 1/24, pantopon gr 1/6 to 1/3 or demerol 35 to 50 mg Morphine should not be used since it increases bronchiolar constriction and depresses the medullary cough and respiratory centers These patients become dehydrated rapidly, and fluid such as 5 or 10 per cent glucose in normal saline solution 1000 cc intravenously every twelve hours, is a valuable adjunct Glucose is essential to replace the liver glycogen stores which have been depleted by epinephrine Should signs of right heart failure supervene, digitalis should be given in the form of digifoline gr 1½ four times a day for four days and this will usually suffice to digitalize the average patient When wheezing and dyspnea are subsiding potassium iodide gr 10 to 15, with the addition of apomorphine hydrochloride gr 1/24 to 1/20 and tincture of lobelia minims 10 to 15 is useful in aiding the expectoration of the viscid tenacious sputum

It may be necessary to resort to bronchoscopy and aspiration of the tenacious sputum and bronchial plugs The author's personal experience in the use of the bronchoscope has been exceptionally successful in several patients with intractable asthma Following the aspiration of considerable viscid secretion and plugs the dyspnea and wheezing rapidly subsided after all other measures had failed It is therefore not wise to wait too long should other methods fail because severe exhaustion or heart failure may later contraindicate the use of this often life saving technic

Outline of Treatment in Status Asthmaticus

1 Hospitalization in a dust free room if possible
2 Force fluids

a By mouth Water, fruit juices, and carbonated drinks
b By intravenous route Dextrose 5 per cent in distilled water or dextrose 5 per cent in saline solution, 3 to 5 liters daily until the patient is hydrated

3 Sedation
Small doses of barbiturates (¼ to ½ gr) chloral hydrate, 2 Gm alone or in combination with sodium bromide, or 4 Gm diluted in 60 cc of warm water given as a retention enema, or 0 5 cc to 1 cc of chlorobutanol given orally

4 Expectorant
Sodium iodide 1 Gm intravenously or saturated solution of potassium iodide, 1 to 2 cc three times a day after meals

5 Bronchodilators
Aminophylline 0 5 Gm intravenously, epinephrine 0 1 cc intravenously in 1 cc normal saline or 0 5 cc hypodermically as circumstances may require when the patient is reactive to same Caffeine alkaloid 3 gr (0 19 Gm) every four hours or caffeine and sodium benzoate 7½ gr (0 5 Gm) every four hours subcutaneously

6 Oxygen or mixture of oxygen 20 per cent and helium 80 per cent when cyanosis is present

7 Avoid at all times the use of morphine, dihydromorphinone, neperdine, and atropine

8 Cortisone 100 mg intramuscularly every twelve hours gradually reducing the dose as the symptoms subside As a maintenance dose 25 mg every twelve to twenty four hours may be sufficient to produce marked symptomatic improvement in intractable asthma

Oral Cortisone tablets, 25 mg every four hours for the first twenty four hours for two or three days, often gives the same relief as when the intramuscular route is used A maintenance dose of 25 mg of Cortisone once a day may be sufficient to maintain complete relief of symptoms On an inadequate dosage or after the Cortisone is discontinued the asthmatic symptoms usually recur

Acthar likewise can be used in very severe cases of status asthmaticus

25 mg every 6 hours for 2 to 3 days
20 mg " " " " " "
15 mg " " " " " "
5 mg " " " " " "

In children doses of 5 to 15 mg every six hours are usually sufficient to relieve intractable asthma These measures merely afford symptomatic relief during the period of severe or intract able asthma

Case Reports

Mrs G S, age 59 was perfectly well until she contracted a cold around Thanksgiving Day when she noticed a distressing cough with short ness of breath, wheezing, and nasal congestion She had a negative family history of allergy Physical examination revealed an obese female who was coughing incessantly There were large hypertrophied tonsils nasal polyps on the left and a few sibilant and sonorous râles along large bronchi The heart borders and tones were normal Blood pressure was 138/100 All skin tests were completely negative

The author referred her to an otolaryngologist because of the nasal polyps and for an investigation of the sinuses The otolaryngologist reported pansinusitis in addition to the polyps and he advised removal of the polyps in order to establish better drainage The polyps were removed and almost immediately thereafter she went into status asth maticus In spite of the use of helium and oxygen and sedation, the course became progressively more severe and it was decided to call in a bronchoscopist At bronchoscopy, an extremely viscid tenacious purulent exudate with sticky plugs was expirated Relief of the status asthmaticus was almost instantaneous and the slight wheezing which persisted was easily controlled by epinephrine in oil An autogenous vaccine was made from the aspirated exudate and a course of injections was given which was followed by considerable improvement She was also given potassium iodide, 15 gr three times a day, for a considerable period of time

This case of asthma was undoubtedly due to an allergy to the products of the patient s own infections in the sinuses and bronchi It should also be pointed out that bronchoscopy was life saving in this case

Mrs. N H, age 22, began to suffer from severe asthma one month prior to the birth of her baby, six months before consulting us She complained of a running nose all through her pregnancy (July through

May) and a sneezing, stuffy, itchy nose Her mother's sister had asthma, but there was no other family history of allergy The patient s presenting complaint was constant wheezing and cough, and examination revealed sibilant and sonorous rales along the bronchi No other abnormalities were noted Intradermal skin tests were positive to cow hair, cat hair, all feathers, sheep wool, orris root, cocklebur, rye, carrot, cucumber, string beans, and hormodendron

Contact was avoided to the epidermals and foods mentioned and hyposensitization was begun to house dust, cocklebur, and hormodendron The patient improved a good deal and was again sensitive to epinephrine and ephedrine products, but she was almost never com pletely free of wheezing and used an epinephrine nebulizer frequently

She remained in this condition for a few weeks, when she developed severe coughing and wheezing which was refractory to epinephrine She was hospitalized and was given, as part of the therapy, 7½ gr of aminophyllin intravenously in 1000 cc of 10 per cent glucose in saline This gave her some relief, but was accompanied by marked cardiac irregularities

Immediately all medication was stopped and she was given two liters of 10 per cent glucose in saline per twenty four hour period, intra venously Her diet was divided into six portions high in carbohydrates and low in bulk, and inhalations of 80 per cent helium and 20 per cent oxygen were maintained for from two to four hours at a time via the B L B mask

Within four hours there was marked relief, and within eight days she was again epinephrine sensitive

Improvement continued rapidly so that she was ambulant within two days

She again came to the office for treatment and felt fairly well although some small sibilant râles were auscultated along the bronchi

Because of the persistence of the wheezing in the face of our elimi nation and hyposensitization therapy, it was decided to do passive trans fer tests in order to detect a hypersensitivity not demonstrable upon her skin Accordingly, we drew blood from her, obtained her serum, and injected it at marked intervals in the skin of the upper arms of her husband, a completely nonallergic individual

Intradermal skin tests on the husband, injecting the antigens into the site where forty eight hours previously we had injected the patient s serum, revealed positive tests to egg, in addition to the other positives that had been obtained in her original test

We then eliminated egg from her diet and continued with our previous

treatment Improvement was dramatic the patient improved so rapidly that it became a problem to induce her to continue hyposensitization therapy

This case illustrates the all important point—that when the allergic regime has been thoroughly followed and yet the symptoms persist one should always do passive transfer tests because it is not uncommon to find that the patient's skin will not react to one or more substances where another individual's skin will reveal the hypersensitivity easily

Mrs L G, age 55, was seen because of asthma of four years' duration, with very little relief There were frequent upper respiratory infections before the onset of asthma The family and personal history were negative for allergic diseases

Examination disclosed wheezing and sibilant and sonorous râles over both lungs, with harsh prolonged expiration There were no abnormal heart findings and the blood pressure was 115/80 Intradermal tests were negative to inhalants foods, and molds

Some improvement occurred with a potassium iodide mixture However, following another episode of an upper respiratory infection, she promptly entered into a state of severe status asthmaticus

Epinephrine 1 1000 and epinephrine in oil did not stop the wheezing and cough Helium 80 per cent, and oxygen 20 per cent were inhaled for three to four hours at one time and had to be used for four days together with ether in oil, equal parts 200 cc per rectum every eight hours, before relief from the severe wheezing dyspnea and cough occurred On a potassium iodide mixture and a change of climate to a warm dry region for several months improvement occurred and no severe asthma has appeared, except for cough and mild wheezing following upper respiratory infections

These patients must guard against repeated 'colds' and exposure in order to avoid asthma and infections in the bronchi Winters spent in warm, dry areas are beneficial for this type of patient

Mrs M G, aged 54, was referred to us for an opinion concerning her complaints of difficulty in breathing, associated with wheezing She was previously diagnosed as asthmatic Physical examination revealed coarse râles along the bronchi, but was otherwise negative Her blood pressure was 160/100, but there was no cardiac enlargement The dyspnea was more pronounced in the daytime and she had no difficulty in active work

except for the wheezing and coughing She had responded excellently to the use of epinephrine and ephedrine products, even in small dosages Complicating the picture was her history of hot flushes, sweating, and nervousness in association with diminishing menstrual flow and skipping of menstrual periods

Intradermal skin tests were positive to cow hair, camel hair, chicken feathers duck feathers, goose feathers hormodendron, alternaria, house dust, barley, casein, cabbage, and carrot

Contact with the offending substances was avoided, and hyposensitization was begun to house dust, cow hair, and the molds

Her wheezing and dyspnea improved rapidly but she still complained that when she was in the house it was worse A trip to the home disclosed a rather dark, damp, dusty atmosphere, and she was advised to change quarters

This was impossible for her to do, so treatment was continued A few months later, severe coughing and wheezing developed which did not respond to epinephrine and the patient was hospitalized by a colleague due to the author s absence from the city at the time The findings were reported to be loud sibilant and sonorous rales throughout the lungs, a blood pressure of 120/90, and a blood eosinophilia of 9 per cent, together with a leukocytosis of 15 000 and a temperature of 100 9° F An electrocardiogram was done because of a suspected acute coronary insufficiency, and the author was called in consultation at this time

The findings were as above except the added fact that the electrocardiogram showed absent R waves in Lead IV, a sign usually considered pathognomonic of an early anterior infarction

This picture was extremely difficult to interpret because the lowered blood pressure would be expected from the asthma, the leukocytosis could result from the use of epinephrine and the electrocardiogram findings could be ascribed to the acute coronary insufficiency accompanying any acute attack of asthma Dr L N Katz has recommended that electrocardiograms not be taken during asthmatic attacks inasmuch as coronary changes are common in the attacks and do not clarify the situation

However, the clinical picture of the case, the marked lowering of the blood pressure, and the persistent leukocytosis with elevated temperature, together with the electrocardiogram, led us to conclude that a silent anterior coronary infarct had occurred

Accordingly all medication was stopped Inhalations of 80 per cent helium and 20 per cent oxygen were begun for four hours at a time and strict bed rest in the upright position was ordered The legs were allowed

to hang down from the bed. Small amounts of 10 per cent glucose in saline were administered slowly intravenously

The patient responded readily and in a few days the wheezing was almost gone, and she complained now of some substernal oppression This latter complaint lasted for only one day At no time was morphine or codein given

We kept the patient in bed for six weeks in the hospital, long after the asthma ceased Serial electrocardiograms taken after the asthma had dis appeared showed typical changes pathognomonic of a healing anterior infarction

This case illustrates the fact that one cannot be too cautious in dealing with middle aged patients with asthma who are also hyper tensive, and that we must consider the possibility of coronary infarcts occurring here as well as in patients who are hypertensive but are free of asthma

Regardless of the difficulty in differentiating a coronary infarct because of the similarities in electrocardiogram and laboratory find ings, the possibility must always be kept in mind that a patient with asthma can also have a coronary infarct

This is extremely important to recognize because the presence of an infarct necessitates the stopping of epinephrine and ephedrine products Also, morphine should not be used here, even in the pres ence of a coronary infarct, sedatives with chloral hydrate or the barbiturates must be relied on instead

PREVENTIVE TREATMENT OF ASTHMA

When one or both parents are allergic, the child should be care fully observed for early manifestations of allergic symptoms such as cyclic vomiting in infancy, vomiting and diarrhea following the eat ing of a food for the first time, urticaria, or infantile eczema These symptoms should be investigated at the earliest possible occurrence both by skin tests and elimination diets It is possible and necessary to do scratch tests and intradermal tests on the back of infants and correlate the results of tests with elimination of the suspected food or inhalant substance Foods in infants and children are more important allergens than inhalants

The mother, during pregnancy, must avoid eating excessive amounts of any particular food but should be advised to eat moderate

amounts of a full diet It has been shown that eating unusual large amounts of a food during pregnancy such as milk or eggs may sensitize the fetus and thus produce reagins in the blood of the infant This explains why the infant develops allergic symptoms the first

ce in a
allergic

and symptoms can be expected at an early age

Preventing an attack of asthma resolves itself in avoiding exposure to extreme cold and wet and avoiding overeating overexertion and irritants of all kinds such as dust animals pets and strong odors

TREATMENT OF THE ACUTE ATTACK

Every allergic patient should be taught how to administer a dose of epinephrine A physician may not be immediately available at the onset of an attack of asthma A reaction may follow a hyposensitizing injection of some pollen food or other substance and the patient may be unable to reach a physician or some food may be eaten which causes severe symptoms If epinephrine is given at once the attack may be shortened whereas the longer the symptoms are allowed to persist without treatment the more prolonged and severe the attack is likely to become

Epinephrine hydrochloride 1 1000 3 to 5 minims subcutaneously is the best for prompt relief of the wheezing This dose may be repeated every twenty to thirty minutes until relief is secured Larger doses produce toxic effects such as marked pallor weakness and rapid heart beat

When the difficult breathing and wheezing are somewhat relieved ephedrine gr 3/8 or 3/4 with or without an added sedative such as phenobarbital gr 1/4 or nembutal gr 1/2 may be prescribed by mouth every three to four hours to maintain the relief Epinephrine 1 100 by inhalation used in a glass vaporizer often affords marked relief Children tolerate ephedrine very well and one half the adult dose can be given to children from 5 to 10 years of age

Care must be exercised in giving ephedrine to older people because it may produce a congestion in an already hypertrophied prostate and result in difficulty in urination or complete obstruction If this symptom appears the use of ephedrine should be stopped

at once and a drug such as propadrine hydrochloride in 3/8 or 3/4 gr. capsules should be substituted.

Potassium iodide, saturated solution, 10 to 15 minims, well diluted in milk or water should be given between attacks for a long period of time. In children, syrup of hydriotic acid, 5 to 10 minims, well diluted in fruit juice, milk, or water, is highly beneficial and can be *given for long periods of time.*

Expectorants, such as ammonium chloride 10 to 15 gr. three or four times a day, Tr. lobelia 10 to 15 minims, apomorphine hydrochloride 1/24–1/20 gr. and ammonium carbonate 5 gr., can be used to liquefy bronchial secretions.

Excessive cough not accompanied by expectoration or wheezing may be controlled by the use of hycodan bitartrate 5 mg. (Endo products) every four to six hours. This preparation is not habit forming and is far superior to codein. Tincture opii camphorata in 10 to 15 minim doses is also useful as a sedative expectorant.

Demerol hydrochloride in tablets of 50 mg. may be used to control the severe coughing paroxysms, without the danger of depressing the respiratory center. The chemical formula is ethyl 1-methyl 4-phenylpiperidine-4-carboxylate. Its effect is similar to that of papaverine but more effective in producing bronchial relaxation and a depression of the muscle fibers. The effect may last from three to six hours, but since this drug may be habit forming it must be used with caution in chronic asthma.

Dilaudid gr. 1/48 to 1/24, and pantopon gr. 1/12 to 1/6 may at times be added to expectorants in order to control severe coughing paroxysms. Morphine and codein are contraindicated in asthma because they cause a depression of the respiratory center and cough reflex.

ROLE OF THE LIVER IN ASTHMA

The work of Whipple has demonstrated that the liver is the sole source of the plasma proteins. This fact is particularly significant in the thorough understanding of the pathophysiology of asthma, for we know that the most probable site of formation of antibodies, both in the *production of immunity* and in *hyposensitization* therapy, is the liver. Indeed, most investigators believe that these antibodies are attached to the globulin fraction of the plasma proteins, viz., immune globulin in measles.

Therefore establishing the condition of the liver is important in the treatment of allergic individuals We must also consider the fact that the asthmatic patient has been subjected to the frequent prolonged use of epinephrine and ephedrine for years and that these drugs are very powerful mobilizers of glycogen in the liver depleting the liver of its glycogen stores Any tendency therefore to obesity hypovitaminosis or exposure to hepatoxic agents such as alcohol becomes highly significant when it occurs in an individual whose liver is being constantly depleted of glycogen a procedure exactly contrary to the dictates of good nutrition

However in many instances this is what we do with the asthmatic patient We limit his diet to prevent overeating and we deplete his liver glycogen stores by the liberal use of epinephrine It is our opinion that varying degrees of liver damage are present in asthmatic patients particularly the middle aged people as evidenced by decreased total protein levels and disturbed globulin ratios

Wagner and Rackemann some time ago did careful sugar tolerance tests on asthmatic patients performing the tests as soon as three hours after the use of epinephrine and found the tolerance essentially normal indicating at least no gross disturbance of carbohydrate metabolism However we believe that a more sensitive test of glycogen stores (such as length of time between administration of phloridzin and appearance of acetone in the urine) would definitely show depletion of liver glycogen Knowing that liver disease is accompanied by depleted glycogen stores and per contra we would not assume too much in considering liver damage in those asthmatic patients who have a history of years of use of epinephrine like products

In our own practice we use 2 to 3 liters of 10 per cent glucose in saline in status asthmaticus and we prescribe a high carbohydrate diet routinely for asthmatics In reference to this Wagner and Rackemann wrote that their patients felt better after the sugar tolerance test and many others use glucose empirically in asthma with good results

To sum up the liver must be given especial attention in asthma because it is the seat of production of antibodies and because it is subject to severe stress during years of depletion of its glycogen stores due to the use of epinephrine

Chapter VIII

Molds

Within recent years, it has become increasingly apparent that mold spores in the air play a role in the etiology of asthma and nasal allergy. Von Leeuwen, in 1924, was the first to suggest that asthma in the humid regions of Holland was due to "Miasmata" or "climate allergens," since he was, at that time, unable to establish positive identity. A year later he reported the relief of patients' symptoms by the use of filtered air. He also found changing a feather sensitive patient to kapok pillows failed to relieve her symptoms, and discovered that the new sensitivity was due to the molds developing on the kapok. Von Leeuwen identified mucor, penicillium, and aspergillus mold as the saprophytic fungi causing asthma, and which he had previously designated as "climate allergens."

The first report of inhalant fungus allergy in America was that of Cadham, in 1924, who described 3 cases of asthma from wheat rust. Cohen, in 1928, found cotton and kapok stuffed pillows, mattresses, and furniture to be sources of house dust antigen. One year later he reported asthmatic patients specifically sensitive to molds isolated from these cotton linters, clinically free from symptoms when these articles were removed. Hansen, in Germany in 1928 found that 15 per cent of his asthmatic patients reacted positively to skin tests with one or more of the aspergilli and penicillia, cultivated from their environment, and in several patients he was able to reproduce symptoms by means of inhaling these molds.

Jimenez Diaz and Sanchez Cuenca demonstrated in 1928, that house dust sensitivity in Spain was often due to molds. In 1934,

Prince Selle and Morrow correlated high plate counts of mold spores and increased symptoms in asthmatic patients with the winds blowing from the swampy regions of Galveston Texas during the winter Feinberg over a five year period—1936 to 1942—in Chicago collected spores by the plate method and observed seasonal aspects in the case of alternaria and hormodendron highest counts occurring during the summer months

Durham in 1937 used the greased slide method to determine the prevalence of alternaria in the United States and concluded that the alternaria belt corresponded roughly to the wheat belt

Grain dust rusts and smuts were also reported by Wittich as the cause of asthma in Minnesota

Monilias and yeasts have also been reported by various observers as etiologic agents in asthma and in 1932 the author reported a child with asthma due to the ingestion of yeast

The greater number of airborne molds come from the out of doors and the soil is perhaps the source of the largest amount Mildew of textiles is due usually to aspergillus or penicillium introduced in raw material during the process of manufacture or acquired during exposure to the air in damp environments Awnings tents draperies window shades wall paper and canvas on walls are potent sources of mold growth in damp districts Upholstered furniture containing cotton or kapok are excellent media for mold growth Wool may be a source of mold fungi mostly penicillium and aspergillus Monilia sitophila is often found in bakeries and homes and may be a potent allergen Luggage gloves shoes leather on chairs and golf clubs frequently become moldy Fresh vegetables and fruits also foods in cold storage frequently become moldy and may cause allergic symptoms in individuals working in packing plants stores and markets Molds rusts and smuts may likewise infest plants in the house or in green houses and affect sensitive patients to produce asthma and nasal allergies

The spores of rust alternaria and hormodendron are more numerous and have a more widespread distribution than all the others

While wind velocity is the most important factor in pollen dispersal the correlation of weather factors with fungus spore incidence is as yet undetermined Areas around farming communities

are probably more abundant in mold grain and rust spores than cities

Many reported cases of inhalant mold allergy have been based upon the finding of positive skin reactions rather than a demonstration of the relationship of symptoms with the actual inhalation of the suspected mold material

The actual number of patients in whom specific mold allergy has been proved by the inhalation of the mold species with symptoms of asthma or nasal allergy resulting has not been large

While many varieties of molds give large intradermal and scratch tests their etiologic incidence in asthma and nasal allergy has not been proven in a large percentage of patients

Fungus spores appear in the air in increasing amounts during July and the early part of August at a time when there is little or no pollen in the air This interval occurs between the grass and ragweed seasons This is consistent with the fact that patients who are allergic to grasses and ragweeds and continue to have symptoms between the seasons are often found allergic to alternaria or hormodendron spores Aspergillus penicillium monilia and chaetomium are less important allergenic fungi

The concentration of mold spores in the air tends to be seasonal mainly from May until November Alternaria and hormodendron spores are the most important ones present in the air in sufficient quantity to cause symptoms The concentration of these spores may reach a peak greater than pollen and can be carried by winds perhaps for a thousand miles or more The greatest concentration of mold spores occurs between September and October usually after ragweed pollen disappears from the air

The substance in the fungi which causes the symptoms is the spore or reproductive element Therefore one should use an extract containing the spores and not the mycelium in testing and treating these patients

The penicillium mold is most frequently found in homes A petri dish containing a modified Sabourand s medium should be exposed for fifteen to thirty minutes in the bedroom occupied by the patient and the mold colonies can then be identified This method is more specific than counts made outdoors and treatment is given to those molds which are actually present in the environment of the patient

Likewise, the atmospheric content of mold spores in the room can be controlled by substituting rubber foam pillows and mattresses or by completely covering these articles with good impervious coverings Old carpets should be removed and only washable cotton rugs sub stituted

The directions given to the patient are the same as for house dust control Basements in the houses should also be conditioned in the same manner in order to cut down the mold activity It is interesting to note that mold sensitivity occurs most frequently in hay fever patients Ocular allergy due to mold spores is not frequent, although perennial rhinitis is commonly due to these agents

Asthma is the most frequent symptom caused by mold spores and perhaps occurs more frequently from this source than following pollen sensitivity

Treatment by hyposensitization similar to pollen therapy is highly satisfactory The antihistaminic drugs are used to relieve nasal symptoms as in hay fever, and asthma is treated symptomatically with drugs until the mold hyposensitivity treatments have been adequately given

CULTIVATION AND EXTRACTION OF MOLDS

Petri plates containing a modified Sabourand s medium (peptone, 30 Gm , agar, 20 Gm and tap water, 1000 cc) are exposed hori zontally outside the window for fifteen to thirty minutes They are then covered and allowed to incubate at room temperature for three or more days depending upon the amount of growth The mold colonies are then identified both grossly and microscopically and individual colonies are transferred to fresh agar plates or slants The subcultures are incubated at room temperature for from one to seven days or until the typical colored hyphae develop The mold is inocu lated into a flask of 10 per cent malt extract in distilled water and allowed to stand at room temperature for approximately one month At this stage, a heavy felt will develop on the surface This is filtered through paper and the residue dried in the incubator for forty eight hours The powdered felt is ground to a fine powder in a sterile mortar and transferred to a sterile tube

Next, add 1 Gm of the dried powdered felt to 50 cc of extracting fluid consisting of 50 per cent glycerine and 50 per cent buffered

saline solution The buffered saline solution consists of sodium bicar bonate 2 7 Gm sodium chloride 5 Gm to 1000 cc distilled water Extract in the refrigerator for one week with thorough shaking at least once a day Filter through a Seitz filter and test for sterility This is 2 per cent stock solution which must be diluted down at least ten times with 5 per cent dextrose diluent before using for intra dermal testing or treatment

THERAPEUTIC USE OF MOLDS

Mold extracts may be purchased from commercial laboratories for testing and treatment It is time consuming and considerable space is required to grow and extract molds They should be culti vated in a separate room from the laboratory because they soon con taminate the floor as well as the rest of the room

In treatment the same schedule is followed as with pollen dust or other inhalants It is customary to start with 0 1 cc of a 1 10 000 dilution and increase the dose by 0 1 cc every three or four days until 0 6 cc is given then repeat this schedule with the 1 1000 dilution 1 100 dilution and finally with the 1 50 dilution When symptoms are relieved the injections are stopped

RESULTS OF TREATMENT

The majority of those sensitive to fungi or molds are also allergic to other inhalants and therefore in routine treatment it is difficult to evaluate results Other inhalant factors are controlled and per haps relief of symptoms may be due to this factor

Chapter IX

Disturbances of the Skin Due to Allergy

ALLERGIC DERMATOSES

Various names have been used to designate the allergic or atopic dermatoses, such as neurodermatitis, flexural eczema, neurodermite, allergic eczema, and lichen simplex chronicus

Brocq a pupil of Vidal, coined the term ' neurodermite" to characterize this disease because of its association with extensive itching and nervousness but without any intention to imply an immediate causal involvement of the central or peripheral nervous system It is for this reason, too, that he subsequently abandoned the term neu rodermatitis' as misleading, and substituted the words "pruritus with lichenification "

The studies of Wise and Ramirez, Rost, Haxtbausen, Urbach, Biberstein, Sulzberger, and Taub and Zakon definitely place neuro dermatitis in the class of the allergic dermatoses The term neurodermatitis should be dropped from the terminology of this condition and the term allergic dermatoses used instead

It usually occurs in older children and young adults who give a positive allergic history and usually have other allergic manifesta tions Scratch, intradermal, and passive transfer studies are generally positive, whereas patch tests are negative Laboratory tests, including basal metabolism, blood chemistry (including calcium and phos phorus), blood counts, and urinalysis show no abnormal findings

Mode of Appearance of the Cutaneous Lesions

At the onset there is absolutely no visible lesion on the integument Gradually the tissues change as a result of scratching, they first lose their normal color and assume a slightly dusky, and at the same time, pinkish, tint, on close inspection the skin is seen to present a finely granular and mottled appearance At this stage it is already possible to discern in certain localities, under varying illumination a sort of flattened, poorly outlined, somewhat glistening, very minute pseudopapule formation Later on these lesions become more pronounced, the tissues assuming a dusky red color or becoming distinctly pigmented, they are roughened and begin to be furrowed by fine crisscross lines The dermis gradually thickens, becomes infiltrated, and the disease finally assumes a truly pathognomonic appearance This process—pruritus scratching pseudopapule formation lichenification—may be limited to only one patch, to a number of circumscribed patches, or may be diffuse and occupy entire segments of the body and occasionally even the entire body

This disease favors certain areas such as the flexor surfaces of the arms, forearms the thighs, flexure surfaces of the knees, the upper part of the thorax, the back the face and especially the forehead, the malar prominences, and the cheeks The attacks of pruritus are usually intermittent paroxysmal and vary with the seasons of the year With this diffuse type of dermatosis patches of the circumscribed type are occasionally found

As a rule, after an active state which may last from a few weeks to several months the affection shows a tendency to disappear through gradual diminution of the pruritus, cessation of the scratching and healing of the lesions However the relief usually lasts only a short time and a recurrence follows, repeating the same process of itching scratching, and lichenification

The microscopic differentiation between the allergic dermatoses and contact eczema consists in the absence of vesicle formation in the epidermis in the allergic dermatoses

The allergen is brought to the skin by the hematogenous route, that is, the capillaries in the cutis The shock tissues are the endothelial cells lining the skin capillaries

Various foods and inhalants may be the causative factors and in

the majority of these patients one finds several substances involved in the etiology (multiple sensitization)

The following case reports will serve best to illustrate this condition

Miss F J, student, aged 20 years Symptoms were pruritus plus lichenification with distribution on the antecubital fossae, neck, front and back, upper part of chest, face eyelids, and forehead, with loss of outer one third of eyebrows Duration was eight years and the patient suspected eggs as the causative factor In the past history, her grand father had asthma The eruption improved in the summer and was worse in winter

Complete tests were done Scratch tests were all negative except a ++++ reaction to silk Intradermal tests were all negative except to silk (++++) Patch tests to silk and some of the commoner irritants were all negative

On avoiding wearing silk since December 9 1932 the pruritus cleared up and at present the lichenification is gone and the skin is soft and smooth Hyposensitization was given to silk extract, starting with a 1 100 000 dilution and continued at bi weekly intervals until a concentrated silk extract was given Locally, only cold cream was used

Some clinicians who do not believe that protein sensitization bears any etiologic relationship in diffuse allergic dermatoses (neurodermatitis) state, as arguments against these findings that local application of the allergen to the skin produces no eczematous reaction This conclusion is erroneous because in the allergic dermatoses we are dealing with cutaneous or blood vessel sensitivity and not with epithelial sensitization as in contact eczema

Miss A E, aged 13½ gave a history of an allergic dermatosis for twelve and one half years Distribution was on the face antecubital fossae, flexure surfaces of elbow, back of neck back, and chest There was a loss of the outer one third of the eyebrows The skin was extremely dry with marked lichenification and intense itching Scratch and intradermal tests were all negative except a ++++ reaction to silk Patch tests were negative In the family history, an uncle had urticaria and the patient's father had some form of eczema

On avoiding wearing silk, the itching improved within two weeks Hyposensitization had to be started with a 1 1,000 000 solution of silk protein extract because of the immense local reactions obtained At the

present time the skin is completely clear and looks natural in every way At one time, owing to an error, a 1 1000 dilution was given instead of a 1 100,000 and, besides a rather severe local reaction, a large eczematous patch appeared on the forehead the next day and extreme itching of the body followed

D H, male, age 20 Allergic dermatoses were present with the typical distribution, and had persisted for twelve years The family history disclosed that one brother had asthma and the father hay fever

Cutaneous tests were all negative, but intradermal tests were positive to wheat and cottonseed Passive transfer tests were done and found positive for wheat and cottonseed Wheat and cottonseed were eliminated from the diet The mattress was covered with an impervious allergic proof encasing The eruption completely cleared up in two months and has remained clear up to date

H J, male, age 17, student Onset of the eruption fifteen years before *Intradermal tests were positive to wheat Passive transfer tests were positive* to wheat On a wheat free diet the eruption cleared up in four weeks

Miss D R., age 14 Allergic dermatosis was present since the patient was six months old One year before seeing the author asthma began

In the family history, the father had hay fever Intradermal and passive transfer tests were positive to egg, oat, and cottonseed Egg and oat were eliminated from the diet, as well as cottonseed, olive oil dressings mustard, candy, and all products containing cottonseed The mattress was covered with an impervious material The asthma cleared up promptly and the skin improved within a period of four weeks

L H, male, age 18, had a typical allergic dermatosis of eight years duration

Intradermal and passive transfer tests were positive to hog hair, sheep wool veal, salmon pineapple, and house dust All foods giving positive reactions were eliminated from the diet Contact to wool was avoided The patient lived in the vicinity of the stock yards he was advised to change his *residence, which he did, and the skin eruption* gradually cleared up The strong skin test reaction to hog hair and dust was an etiologic factor by inhalation

Miss A K, age 17, had an allergic dermatosis of five years duration and vasomotor rhinitis during the previous year She had had quartz lamp and roentgen therapy, thyroid medication, and autohemotherapy for a considerable time, without improvement

In the family history, one brother had hay fever

Intradermal and passive transfer tests were positive to silk Patch tests were negative to silk and various cosmetics

On avoiding wearing silk and substituting cotton, the skin cleared up in a few weeks and hyposensitization was started to silk protein extract Because this patient also had a vasomotor rhinitis and silk was the only protein giving a reaction a small amount of powdered silk protein was blown into one nostril and some inert talc was blown in the other nostril as a control Within a few minutes marked itching was complained of, followed by a violent sneezing and watery nasal discharge from the nostril into which the silk protein had been blown There was also considerable local irritation and redness on that side

It has been further demonstrated (Sulzberger and Vaughan) that when blood is drawn from a silk sensitive patient (passive transfer) and injected into the skin of a normal nonallergic individual, and forty eight hours later a small pinch of powdered silk extract is blown into the nostril of this nonallergic individual, within eighteen minutes a large local reaction will appear over the passive transfer site

It is obvious that substances in the air or clothing worn by the patient, may be absorbed through the respiratory tract, and thus enter the blood stream and reach the skin If the absorption is through the lungs the route to the skin is shorter and more direct and without as much possibility of denaturization of the allergen as is the case when absorption occurs through the gastrointestinal tract If, in a given case of atopic skin sensitivity, both foods and inhalants elicit positive skin reactions, both groups must be eliminated and the patient should be hyposensitized to both foods and inhalants before one can expect a complete cure

Local Treatment

The antihistaminic drugs are helpful in allaying severe itching Frequently a combination of pyribenzamine 50 mg and antistine 100 mg in capsules, given every four hours relieves itching more adequately than either one of these drugs used alone because of the synergistic action Mild tar ointments particularly crude tar such as Daxalene (Dow chemicals) in ½ to 1 per cent strength in plain white vaseline, are used locally for severe itching Soaps are avoided and

one of the soapless detergents substituted Boric acid 2 to 4 per cent in aquaphor or plain petrolatum often counteracts the dryness of the skin Pyribenzamine 2 per cent ointment, benadryl 2 per cent ointment, thephorin 5 per cent ointment, or trimeton maleate cream 3 per cent may be used locally for pruritus

For severe itching, the following prescription is useful

Zinc oxide	25 0 Gm
Talc	25 0 Gm
Glycerine	50 0 Gm
Aqua	50 0 cc

Sig Shake lotion to be applied frequently

At one time unsaturated fatty acids such as maize oil and linseed oil, were advocated in atopic dermatoses but no results were obtained in a series of patients investigated by the author and Dr Zakon Some patients developed asthma and oily cysts with furunculosis Their use has been discontinued since these dangers were pointed out

INFANTILE ECZEMA

Infantile eczema, atopic dermatitis allergic eczema or simple eczema are synonymous terms used for the most important skin disease of infancy and childhood

The chief characteristics are as follows

1 A hereditary predisposition which can be elicited by a history of some allergic disturbance in a parent, grandparent or blood relative

2 Hypersensitivity of the deeper layers of the skin (cutis) to protein or protein like allergens Scratch or intradermal tests usually produce immediate wheal like type of reactions Patch tests are usually negative

3 The substances responsible for the eruption may reach the skin through the blood vessels and skin capillaries by means of inhalation ingestion or absorption after direct contact

4 Passive transfer tests are often positive This method can be used when the patient s skin is too extensively involved or too irritable to be tested directly

5 As the child with eczema grows older, typical sequelae may occur, such as recurrent upper respiratory disorders, pollinosis, and

asthma Frequently these disorders accompany the atopic dermatitis

Atopic dermatitis (infantile eczema) begins early in infancy from a few weeks to several months of age It usually starts on the cheeks and may follow a seborrheic dermatitis so gradually that it may be quite difficult to determine where one condition ends and the other begins Often the two conditions are present at the same time As the eczema spreads the extensor surfaces of the wrists and ankles and finally the trunk are involved The palms and soles are usually free

Atopic dermatitis can be divided into three main groups the acute which includes atopic erythroderma and the subacute forms the chronic and atopic dermatitis by contact

Acute and Chronic Atopic Dermatitis

There are four principal stages in the development of the acute and subacute forms of atopic dermatitis One or all of them may be present simultaneously depending upon the degree of congestion and edema of the skin

1 The congestive stage with simple reddening of the skin commonly known as erythematous eczema If this persists hypertrophy of the squamous cell layer of the skin may be stimulated producing the so called squamous eczema

2 Vesicular eczema with typical minute intra epidermal vesicles These may be superimposed on small itching papules which when present are known as papular eczema

3 Moist or weeping eczema results from vesicles that coalesce and rupture Serum exudes on the surface of the lesions and dries to form the next stage or crusting eczema If the atopic dermatitis persists it tends to localize in the cubital and popliteal fossae around the wrists and ankles especially the extensor surfaces around the neck and at times in the axillary folds The forehead and face may be involved but the trunk is rarely affected This stage is known as chronic atopic dermatitis or flexural eczema and usually appears in older children or adults It may be the end stage of acute atopic dermatitis or appear initially as the chronic stage

Lichenification or exaggeration of the normal cross markings of the skin is common with considerable thickening and roughness resulting Atopic erythroderma a term described by Hill represents the highest degree of atopic dermatitis in infancy In this condition

there is a generalized eruption usually with some vesiculation and profuse scaling A marked general lymphadenopathy with cold blue feet is characteristic.

Passive transfer tests are useful guides as to what foods and inhal ants should be eliminated These infants eventually improve and enter the stage of chronic atopic dermatitis

Atopic Dermatitis by Contact

The lesions are produced by contact with substances which act as allergens A child may be so highly sensitive to egg that the mere contact with egg on the lips or face may result in an eruption This is due to transepidermal penetration of the allergen

Other substances such as silk wool tomatoes oranges or other foods may cause atopic dermatitis by contact in children who are highly sensitive to these substances These allergens frequently give positive patch tests as well as intradermal or scratch tests Soaps cleaning agents creams and oils used on the infant s skin can be tested by means of the patch tests

Treatment

The treatment of atopic dermatitis is not completely satisfactory The disease is usually self limited with a tendency to spontaneous remissions and eventual recovery regardless of therapy However it is important to attempt to find the etiologic factors since one is not able to foretell which child will outgrow atopic dermatitis and which one will not The suffering endured by the child and parents may likewise inflict a tremendous psychic trauma so that every effort should be made to clear the child s skin as soon as possible

The presence of atopic dermatitis is also an indication that the child is an allergic individual The skin manifestation is only one phase of a cycle that may progress involving various shock organs with varying degrees of intensity for the balance of the patient s life

The object of treatment therefore should be to relieve the eczema and also to outline a way of life that may prevent the future development of other serious allergic conditions such as asthma The fol lowing measures should be considered in treatment (1) Prophylactic (2) environmental control (3) dietary control (4) local treatment

(5) systemic treatment and (6) specific treatment which consists of elimination and hyposensitization against the causative allergens

Prophylactic Treatment Grulee and Sandford made a survey of some 20 000 infants at feeding stations in Chicago and noted that the incidence of eczema was lowest among infants who were partially breast fed while artificially fed infants showed an incidence of eczema seven times as great This study should be sufficient indica tion of the need for breast feeding infants born in allergic families

Enviromental Control It was formerly believed that foods played the dominant role during infancy as a cause of atopic dermatitis Now it is quite generally accepted that direct contact of allergens with the skin or transepidermal penetration as well as allergens which reach the skin via the blood stream after inhalation are of equal or greater importance Quite frequently a combination of these factors is present since multiple sensitivities are the rule rather than the exception Likewise atopic dermatitis and contact derma titis may have been too sharply separated in the past when in reality they may be caused by the same allergen

The characteristic distribution of atopic dermatitis with lesions worse on the face on the arms below the elbows and on the legs below the knees suggests a possible contact origin In some cases house dust could act by inhalation and also by contact The beneficial effects of hospitalization often dramatic have been attributed to avoidance of house dust as well as of other environmental allergens

Hyposensitization with house dust extract often gives excellent results One is therefore justified in advising an environment as free from dust as possible Specific directions should be given for avoiding feathers silk wool clothing dyes soap animal pets and toys with these substances Nylon celanese rayon and tightly woven cotton cloth can be substituted in place of wool and silk

Local Treatment Soap aggravates most patients with atopic der matitis Its degreasing and keratolytic action may favor the pene tration of environmental allergens in the skin and thus cause further irritation Mineral oil vegetable oil and sulfonated oil may be used to clean the skin but their disadvantage is that they produce no suds The newer wetting agents derived from Lauryl alcohol are so far the most satisfactory One of their disadvantages is that dryness of the skin is produced and that they may also act as sensitizers espe-

cially in adults Ar Ex and Marcelle have a liquid detergent Phiso-derm is also liquid while Lowila cake and Dermolate are bars

Colloidal baths are helpful in soothing and clearing the skin They consist of adding one or two cups of cornstarch and one or two cups of baking soda to a tubful of water Tar baths consisting of liquid Carbonis detergens N F two cupfuls to a tub of water or Almay tar bath may be useful

In the acute or exudative stage physiologic saline solution applied as wet dressings is soothing Burow s solution is applied as a 1 20 dilution of aluminum acetate or Domeboro tablets or powder (Dome Chemical Co) 1 tablet dissolved in 8 oz of tap water 1 10 or 1 tablet dissolved in 16 oz of tap water 1 20 Boric acid as a half or full saturated solution can be applied for its mild antiseptic and astringent action although it should not be used over long periods since there is some danger of absorption and poisoning in young infants Boric acid may also act as a skin sensitizer Potassium per *manganate 2 5 Gm in distilled water 1200 cc ½ teaspoon to 1* pint of water (1 1° 000 solution) is mildly astringent and disin fectant when applied as wet compresses

Boro salicylated solution (Thiersch s solution) consists of boric acid 12 0 Gm salicylic acid 2 0 Gm and distilled water q s ad 1000 cc It is applied undiluted as wet compresses

Raw or oozing areas may be painted with a 2 to 4 per cent aqueous solution of gentian violet medicinal and covered with calomine lotion with or without phenol

The 1 2 3 ointment consisting of one part aluminum acetate solu tion (Burow s solution) two parts wool fat and three parts zinc without salicylic acid may be soothing in the acute stage Where the skin is sensitive to wool Hydrosorb greaseless ointment base and Ar Ex multibase may be substituted for wool fat

Tar in various ointments is used in the subacute and chronic stages There are two varieties of tar the black and the white Of the black Daxalan (Dome and Co) in 1 to 3 per cent strength with petrolatum alba is often the most helpful It is wise to start with ½ to 1 per cent Daxalan in the subacute or early chronic stage and in the advanced chronic stage where considerable scaling and thick ening of the skin is present 3 per cent is preferred Of the white tars

Supertah in 3 per cent strength is useful at times It may likewise be used in 5 to 10 per cent strength

Vioform (7 iodo 5 chloro 8 hydroxy quinoline) introduced into this country by Sulzberger and his co workers is occasionally helpful in atopic dermatitis especially if the skin is superficially infected It is more useful in seborrheic dermatitis It may be used in 1 to 3 per cent strength added to petrolatum alba as a base

Systemic Treatment The antihistaminic drugs are useful in relieving the intense itching which is one of the most disagreeable symptoms Pyribenzamine benadryl and thephorin may be used effectively Benadryl and pyribenzamine give relief during the night and at bedtime because of the drowsiness they produce

A sedative mixture may be given for the itching This consists of chloral hydrate 1 0 sodium bromide 1 5 and syrup simplex q s ad 30 0 One half teaspoonful of this mixture in water given three times a day may be used effectively when the antihistaminic drugs fail

Dietotherapy Direct skin tests are usually the most satisfactory means of determining the inhalants or foods responsible for the eczema in infants and young children Scratch testing is usually done first although intradermal tests may be made care being taken to avoid generalized reactions by making sure that each intradermal test is preceded by a negative reaction to a scratch test

In the case of milk sensitivity a difficult problem presents itself since milk is such an important food in infancy that depriving a child of it for any length of time would endanger nutritional balance Milk is also a component of so many foods as to make it difficult to eliminate it entirely from the diet Milk contains three proteins casein lactalbumin and lactoglobulin The overwhelming majority of infants are sensitive to the lactoglobulin and lactalbumin fractions and only a few are sensitive to the casein fraction The casein is intimately associated with the lactalbumin fraction and since casein is coagulated in the stomach by hydrochloric acid and pepsin the only allergens passing the pylorus are the albumin and globulin fractions contained in the whey Only albumens in a highly soluble form can pass through the intestinal wall and circulate as active allergens It is for this reason that evaporated milk is the best substitute for infants allergic to cow s milk During the heating process

involved in making evaporated milk the albumen fractions are coagulated and thus are not able to act as allergens

A cow s milk substitute such as soy bean milk may be helpful In case of sensitivity to soy bean one of the meat base artificial milks such as Armour (Gerber) and Swift may be used with good results Goat s milk may be used successfully if the infant is sensitive to lactalbumin which is species specific However some are sensitive to casein which is the same composition regardless of the animal

A simple elimination diet may be used before skin tests are done Such a diet would consist of one of the cow s milk substitutes such as soy bean milk or protein meat base a simple cereal as oat meal two fruits apple and pear two vegetables carrots and string beans chicken or capon and vitamins A and D (Provatal Wyeth which does not contain cod liver oil) and vitamin C in place of orange juice

If after a trial diet of one week the child obtains some relief one new food is added each week according to the need and tolerance If the child does not do well variations may be made in the con stituents of the diet However at this point cutaneous testing is helpful in enabling one to select a diet which has the best chance of determining the offending allergens Foods that are positive on tests should be avoided

ACNE

In 1931 Rowe reported the cure of a long standing case of acne with the use of the elimination diet

White in 1934 reported a series of 32 patients with recurrent papular and papulopustular eruptions of the body involving the areas in which acne vulgaris is usually found He considers these lesions as acneform because there are no comedones no seborrhea of the face or scalp and they do not respond to the usual acne treat ment These patients were found sensitive to various foods such as chocolate milk wheat oranges tomatoes and nuts *Multiple sensi tivity* was usually present and Rowe s elimination diets were more helpful in the diagnosis than skin tests

Gunningham and Mendenhall studied 42 patients with acne who reacted by skin tests to foods Avoidance of the foods which were

positive on skin tests relieved a large majority of these patients, there being only 13 per cent who were not benefited

My own experience with acne has been very satisfactory This is especially true in those who have associated allergies such as hay fever, asthma, perennial rhinitis, migraine, or urticaria Foods are an important factor and skin tests, particularly intradermal tests with potent food extracts, are of great diagnostic help Rowe s elimination diets are helpful when tests to foods are negative Chocolate, nuts, tomatoes, sea foods, condiments, iodized salt, and vitamins of the A and D group (cod liver oil) are frequent offenders X ray therapy and endocrine products have yielded rather poor results

PURPURA

Allergic purpura due to foods or drugs must be recognized as a clinical entity Various observers report foods as the etiology of purpura and thrombocytopenia These conditions can be produced by the ingestion of foods to which the patients are allergic and, upon eliminating these foods, will completely disappear Young girls between the ages of 14 to 17 years are more frequently affected Wheat, eggs, milk, onions, nuts, and members of the cabbage family are frequent offenders

One of my patients, age 15, who had frequent attacks of purpura of the skin with rectal and vaginal hemorrhage and who was found sensitive to wheat by intradermal tests, completely cleared up on strict wheat elimination Another girl of 12 with purpura and seasonal hay fever, found sensitive to milk (lactalbumin) by intradermal skin test, became symptom free on a strict milk elimination regime

Drugs such as aspirin quinine, ergot, arsenicals, phenobarbital, sedormid and iodides have been reported as a cause of purpura Their prompt elimination results in rapid disappearance of the condition

CONTACT DERMATITIS

The epidermal or outer layer of the skin is involved in contact dermatitis due to exposure to various antigens Metallic salts, chemicals, and oily resins of plants, flowers, and weeds may sensitize the epidermis by contact The oil fraction is soluble in the oil of the skin, while various chemicals may penetrate the horny layer of

the epidermis and have an affinity for the epidermal cells The epidermis has no blood vessels and the allergen cannot be brought to the skin by the blood vessels as in the allergic dermatoses The lesion produced as a result of contact in these patients is a vesicle The epidermal cells become swollen with the formation of fluid between the cells, thus resulting in vesicle formation in the epidermis Weeping exudation, and crusting may develop later and, finally, hyperkeratosis with lichenification and thickening of the skin occurs, resulting in a rough, thickened, and leathery appearance

The term dermatitis venenata' had been applied to this condition by some, but this name is undesirable because it would indicate a poison or toxic factor The condition is actually an allergic one produced by contact with the epidermis The exposed surfaces of the body, as the face, hands, and neck, are usually affected first, although the allergen may be carried by the hands to other parts of the body

In this group we find various vegetable and plant oils such as poison ivy, oak, sumac, primrose, ragweed, and gladiolus bulbs Occupational contact dermatitis may result from contact with chemicals, metals fur, dyes leather, cosmetics, and drugs

Contact Dermatitis Due to Drugs, Chemicals, and Cosmetics

Almost any drug or chemical may cause a dermatitis in one predisposed to cutaneous sensitization, if sufficiently prolonged exposure occurs Chemicals used in various occupations may cause a contact dermatitis after repeated use, and the list of chemicals is too long to mention, although some typical ones will be included here

Barbers quinine, sulfur, resorcin, and mercury in hair tonics
Dentists novocaine and cocaine
Druggists ipecac, quinine, novocaine, cocaine lycopodium
Exterminators arsenic, pyrethrum, formalin and copper sulphate
Furriers paraphenylenediamine dyes, para amido phenol dyes aniline black, naphthalene, paradichlorobenzene, arsenic, furs, and skins
Gardeners insecticides, fertilizers lime, arsenicals, and plants
Grocers flour, soy and cottonseed meals, sugar
Jewelers sawdust, cyanide, alcohol

Nurses Formalin lye soaps medicated alcohol bichloride of mercury and other antiseptics
Painters linseed oil aniline dyes turpentine arsenic varnish
Metal polishers bichromate turpentine oxalic acid
Printers colored inks arsenic dyes
Surgeons antiseptics used on the hands bichloride of mercury lysol medicated alcohol rubber gloves
Housewives strong soaps ammonia abrasives and cleaners wash powders household rubber gloves

Ephedrine may cause contact dermatitis around the nose and upper lip following prolonged local use in the nose

Quinine in hair tonics may cause a vesicular dermatitis of the scalp face and neck Likewise contraceptive suppositories or jellies containing quinine may produce a dermatitis of the penis scrotum and vagina

Lanolin calmitol mazon ointment liquid arvon (an arsenical) resorcin in hair tonics and salicylic acid have been reported as a cause of severe contact dermatitis in various parts of the body

Dyes used in dresses clothing leather goods shoes socks and cosmetics are frequent causes of dermatitis

Clothing exposed in a closet of paradichlorobenzene cakes to prevent moth infestation may cause contact eczema

Dress shields may cause an irritation in some people because of the chemicals used in processing them Rubber goods such as rubber gloves rubber in dress shields condoms and rubber panties may also be irritating Sulphur monochloride used in vapor curing these products often leaves hydrochloric acid as a byproduct which is a strong irritant Perspiration plus friction moisture and heat aids in dissolving the acid irritant into the skin

Irritation from these materials can be avoided by soaking the rubber material or gloves in a solution of sodium carbonate or soap solution and rinsing thoroughly

Dermatitis of the eyelids may be due to metal or horn spectacle rims creams nasal sprays eye washes face powders wave set preparations perfume nail polish and face lotions

Common brands of toilet soaps liquid soaps and household soaps containing strong alkalies or lye are frequent causes of dermatitis

A light solution of soap suds should be used in patch testing in order to avoid nonspecific irritant reactions

Allergy from Sulfonamide Drugs Cutaneous manifestations following the use of sulfonamide drugs may be of the following characteristics Erythema nodosum urticaria and maculopapular and exfoliative dermatitis

Fever is by far the most common allergic response occurring in almost 50 per cent of patients between the fourth and tenth day after the onset of treatment It disappears rapidly following discontinuance of the drug Polyarthritis peripheral neuritis conjunctivitis and even interstitial myocarditis have been reported Chills and eosinophilia are often present Sulfanilamide and sulfathiazole cause reactions more often than sulfadiazine sulfapyridine or sulfamerazine (sulfamethyl diazine) Approximately 5 per cent of patients receiving various sulfonamides develop febrile reactions during the first course of treatment whereas 15 per cent develop fever reactions accompanied by dermatitis and conjunctivitis following two courses of the same drug If one of the other sulfonamide drugs is used during the second course of treatment fever reactions are reduced to only about 3 per cent It is therefore advisable to use a different sulfonamide in a second course of treatment in order to cut down the incidence of reactions from these drugs Sulfadiazine has at times also produced a thrombocytopenic purpura which cleared up following withdrawal of the drug

The quantity of the drug used is an important factor in the incidence of these reactions—the larger doses of 4 to 5 Gm a day for five to six days are followed by the largest number of reactions whereas the smaller amounts as 2 Gm a day given for the same period of time rarely produce reactions

Patch tests are frequently positive in the dermatitis reactions and in the contact dermatitis resulting from the local application of the drug to the skin

An intradermal test has recently been described by Leftwich which consists of drawing 20 to 30 cc of blood from a patient who has been receiving sulfathiazole (3 Gm a day for seven days) showing an average blood level of 4 mg per cent of free sulfathiazole The blood is allowed to clot and is then centrifuged for twenty minutes at high speed The serum is removed by a pipette using sterile

precautions, and is subjected to the Kahn and Wassermann tests Next, 0 05 cc. of this serum is injected, intradermally, into the skin of the suspected sulfathiazole sensitive patient, and a typical wheal results within fifteen minutes Large wheals are produced, measuring 12 to 18 mm, with pseudopod formation, as is an accompanying erythema, measuring 30 to 40 mm

In this study, blood was obtained from patients who had received sulfonamide therapy for from one to fifteen days and the percentage of the blood sulfonamide level had no influence on the percentage of positive tests obtained According to Leftwich, 90 per cent of sulfonamide sensitive patients gave strong positive reactions with this technic It has been suggested that the sensitizing antigen may be a sulfonamide plasma protein combination, the sulfonamide being a hapten This test has considerable merit and may prove extremely helpful in testing to other drugs that produce various allergic phenomena

A fuller discussion of drug allergy is presented in the next chapter

Cosmetic Sensitivity The universal use of cosmetics has resulted in the occurrence of a widespread sensitivity to the various ingredients, with a great diversity of symptom manifestations

A dermatitis affecting the eyes, face, and neck is typical of nail polish whereas orris root, rice powder, arrowroot, and corn starch in face powder may produce nonseasonal hay fever and asthma

The importance of a complete history cannot be too greatly emphasized It is important to determine the exact onset of the difficulty, especially if it can be correlated with the use of some new product

The following substances in cosmetics may be a causative factor in producing a dermatitis Perfume containing various essential oils and coal tar derivatives may produce a dermatitis in some people, especially when exposed to the rays of the sun These substances may also be responsible for nonseasonal hay fever, urticaria, and asthma in some individuals Sensitivities may also occur from other ingredients found in perfumes, such as citrus oils, flower extracts, animal substances, gums, barks, and mosses

Lipsticks contain various aniline dyes which produce a cheilitis and even gastrointestinal symptoms, such as colitis, from swallowing the dyes with the saliva Lipsticks and face creams may contain

bismuth compounds, cocoa butter, cocoanut oil, cottonseed oil, castor oil, oil of bergamot, and oil of cassia, and may also contain various gums, such as karaya, quince seed, tragacanth, and arabic. Face and talcum powders may contain orris root, wheat and rice starch, lycopodium, and barium sulphide.

Beeswax, lanolin, almond oil, and methyl heptine carbonate are other components of lipsticks, rouges, creams, and lotions

Indelible dyes, chiefly tetrabrom fluorescin, an aniline dye, are found chiefly in lipsticks, whereas lakes and other chemical dyes are present in powders and rouges

In obtaining the history of cosmetic sensitive patients, it is likewise important to investigate the possibility of similar allergens which may be present in toothpastes, tooth powders, chewing gum, gargles, and medicated creams Essential oils of peppermint and spearmint are found in candies and chewing gum Menthol, eucalyptol, and thymol may be present in dentifrices, antiseptics, gargles, throat lozenges, and medicated jellies Oil of clove or clove extract may be found in foods—Virginia ham, cooked fruits, and candies Citrus oils are present in lemons, oranges, limes, and grapefruit

In a suspected cosmetic allergy, patch tests are done with the various suspected substances and an attempt is made to reproduce the original reaction on the skin, upon a different site from where the original manifestation occurred A small amount of the material is placed on the skin, usually the back, arms, thigh, or abdomen, and is covered with a small piece of cellophane, which is attached to the skin by adhesive strips The patch is left on the skin for forty eight hours—although, should a reaction occur before this time, such as itching, burning, and redness, it should be removed at once

In various eczemas and cases of dermatitis of the face, patch tests done on other parts of the body with the offending substance may be negative and it may be necessary to apply the tests on the site of the eruption itself

There are several excellent hypoallergenic cosmetics on the market, such as Marcelle, Ar Ex, and Almay Special formulas are available and can be ordered to exclude the substance that causes the sensitivity If perfume is the sensitizing agent in a lipstick, an unscented one can be ordered If sensitivity to the indelible dye is present, a lipstick without the indelible dye can be used If the

patient is sensitive to the coloring matter in rouge substitute colors may be tried

Where castor oil is found to be the cause of the irritation liquid petrolatum may be substituted The combination of Dibrom and tetra bromfluorescin with castor oil may produce a sensitizing agent of considerable potency During the testing period all cosmetics should be eliminated

Nail Polish Dermatitis Patients sensitive to nail polish are affected by a severe itching dermatitis which involves the eyelids face and neck The skin adjacent to the fingernails is never involved Patch tests are positive to the colorless lacquer as well as to the whole polish Tests should be applied to the V of the neck because at times patch tests may be negative when applied to the back The undiluted polish is used on the patch The dye is not the offending agent but a formaldehyde sulfonamide resin and the nitro cellulose solution (basic lacquer) contained in the nail polish are the important sensitizing agents Patients improve rapidly with avoidance of the nail polish

Colorless nail polish will likewise affect these patients since it contains this same resin Hyposensitization is not possible and complete avoidance of these varieties of nail polish must be insisted upon to avoid recurrences The usual powder nail polishes which are applied with a buffer are the best substitutes

Common cosmetic irritants and allergens with their sources and symptoms are outlined in the Appendix

Contact Dermatitis from Weeds and Plants

Poison ivy and oak and primrose are the most important plants that produce an acute severe dermatitis or a chronic eczematous eruption depending upon the sensitivity of the patient and the degree of exposure to these plants

The acute vesicular dermatitis is due to a high degree of sensitivity of the patient or to a massive or prolonged exposure of a moderately sensitive individual These people are incapacitated for a variable period of time and exposure to the offending plant may be periodic The eruption caused by poison ivy which is a violent skin sensitizer is an example of a recurrent severe type of acute dermatitis

Contact dermatitis of plant origin may also be ch

throughout the growing season of the plant It is often perennial with slight remissions occurring during the dormant season There is usually erythema marked itching and lichenification with thickening of the skin from persistent rubbing and scratching Exacerbations with vesiculation weeping and crusting may follow prolonged or massive exposure to the plant

Dermatitis from Flowers and Shrubs These plants usually affect housewives and florists The eruption generally occurs on the hands forearms face and neck In handling flowers and shrubs the housewife gardener or florist comes into intimate contact with large amounts of the oleoresins of these plants for a considerable period of time

The important skin sensitizing plants in this group are primrose (*Primula Abconica*) daisy (*Pyrethrum*) and the *chrysanthemum* family Narcissus tulip iris carnation zinnia and shasta daisy are also common irritants

Dermatitis from Vegetables and Fruits Contact with vegetables and fruits may cause an acute or chronic type of dermatitis Housewives grocery clerks truck gardeners and cooks are usually affected The hands are usually affected and other parts of the body are spared since frequent washing of the hands particularly among housewives reduces the possibility of transferring the oleoresins to other parts of the body

Spinach radishes potatoes tomatoes oranges carrots lemons grapefruit mustard and turnip greens corn grapes and figs may produce this type of dermatitis

This type of contact dermatitis may also be of the patchy variety and patch testing with the various vegetables handled by the patient should be done A dermatitis about the mouth and lips may also be caused by eating fruits

Dermatitis from Weeds The eruption frequently involves the face neck hands forearms legs and ankles although in some patients it may involve the entire body Erythema with marked itching and thickening of the skin generally occurs Daily contact with weeds as in cutting and handling may produce vesiculation and edema of the skin Lichenification of the flexures of the forearms and knees is typical of weed eczema The eruption usually begins in early summer and lasts until a killing frost occurs It may appear

seasonally at first corresponding to the growing season of the weed later extending further in the winter and finally becoming perennial with exacerbations during the summer months

The important weeds causing a dermatitis are the short ragweed (Ambrosia elatior) bitterweed sneezeweed marsh elder (Iva angustifolia) and firewheel (Gaillardia pulchella)

The moderate skin sensitizers are Bermuda grass crab grass cocklebur and broomweed Infrequent skin sensitizers are giant ragweed milkweed horse mint and the cratons

The dermatitis producing fraction is the oleoresin which appears on the leaves stems and flowers as fine globules of oil which can be seen with a hand lens These oleoresins are usually quite sticky and adhere tenaciously to the skin and clothing

House dust oil and thresher dust oil have also been found to be a factor in certain patients suffering with contact dermatitis Stroud studied 3 patients who had a contact dermatitis of the hands while working around threshing machines Dusts brushed from threshing machines were extracted and the oil residue was used for patch tests Positive reactions were obtained in these patients and the dermatitis cleared up after several intramuscular injections of the oleoresin

Method of Applying Oleoresins Shelmire dilutes the various plant oleoresins in acetone and places them in 4 cc cork stoppered vials Applications are made on the back with the moistened end of the cork and when the acetone evaporates a small quantity of crude resin remains in contact with the skin These patch tests are not covered and the patient is advised not to bathe for twenty four hours Should itching burning and erythema develop before twenty four hours the patient is advised to report to the office

The author prefers to patch test with a small portion of the leaf and stem of the plant and cover with a patch for twenty four to forty eight hours Should itching or burning and smarting occur sooner the patch should be removed at once A one hour contact period with the leaf will usually result in a positive reaction and severe irritative local reactions with a generalized flareup of the skin may thus be avoided

Treatment of Plant Dermatitis Once the etiologic diagnosis is made further contact with these plants can be avoided and the dermatitis will be alleviated

Florists, housewives, and gardeners can protect the hands by the *use of rubber gloves or other protective* gloves when handling vegetables, fruits, or plants to which they are sensitive Primrose plants must be excluded from the house

In poison ivy, oak, and ragweed dermatitis, the use of intra muscular injections of the oil extract, 0 5 cc to 1 0 cc every three to four days, results in marked alleviation of symptoms Itching is relieved and the dermatitis clears up rapidly, providing further exposure is avoided

Prophylactic injections of 0 5 to 1 0 cc of the oleoresin of poison ivy or oak, given in the spring months of the year, once a week for three doses, will in a large majority of patients prevent the recur rence of the dermatitis The oral administration of the oleoresin of poison ivy has been tried and found ineffective Pruritus ani has been observed after its use and also perioral dermatitis

Case Reports Mrs H E, age 56, housewife, came in because of a severe itching dermatitis involving the face, neck, fingers and hands for a period of one month The eruption started with small vesicles on the fingers and then the eyes, face, and neck became involved Swelling itch ing, and burning were severe Several dermatologists were consulted and the eruption became even more severe, in spite of various local and roentgen therapy

This patient was seen on April 21, 1943 with an extensive erythematous and edematous rash with fine vesiculation involving the hands, fingers, eyes, face, neck, and forearms In the history it was noted that she cared for several plants in the house, consisting of a coral plant pussy willow, philodendron, cyclamen and primrose The plants had been in the house for some months but the primrose plant was brought to the house on February 18, 1943—just about four weeks preceding the dermatitis

Patch tests were performed with the leaf, stem, and flower of the vari ous plants and twenty four hours later there was a severe local reaction with itching and burning and a generalized increase in itching and burn ing of the hands and face appeared The patch test was strongly positive to the leaf, stem, and flower of the primrose plant

On further history, it was disclosed that the primrose plant was kept on the dining room table for one day, and later was moved to an en closed porch The plants were trimmed and soaked frequently in the kitchen sink and she noted water blisters with itching on the fingers after a short period of time

The primrose plant was removed from the house and complete disappearance of the dermatitis followed within a week There has been no recurrence to date

R T, male, age 14 student Poison ivy dermatitis began for the first time in the latter part of July, involving the hands legs, forearms and face Itching vesiculation and edema of the skin was intense The eruption subsided following two 1 cc. intramuscular injections of poison ivy extract in oil on two successive days No recurrence occurred the rest of that summer The next summer there was a similar recurrence of the dermatitis which was rapidly controlled by two injections of 1 cc. of the oil extract intramuscularly, on two successive days The following year two prophylactic injections of 1 cc. of the oil extract were given intramuscularly a week apart and there was no recurrence of the dermatitis that year Uniformly good results occurred in other patients treated both actively and prophylactically with the poison ivy oleoresin extract in oil given intramuscularly

DERMATOLOGIC ALLERGIC FORM

1 Name ________________ Age ____ Occupation ______________

2 List the materials with which you work
   a Chemicals
   b Drugs
   c. Plants
   d Furs
   e Dyes
   f Foods

3 Describe the surroundings in which you work

4 Home contacts
   a Colognes and perfumes
   b Cosmetics
   c Soap
   d Hand lotions
   e Rubber gloves
   f Washing powders
   g Alcohol
   h Hair tonics
   i Dress shields
   j Nail polish

k Wave set preparations
l Plants
5 What drugs or ointments have you used within the past month?
6 Description of lesion
a Location of the lesion
b Nature—dry or moist, erythematous papular, vesicular, weeping crusting itching lichenification
7 How long have you had this condition?
8 Family and personal history of other allergies
9 What treatment have you had for this condition?
a Internal
b External
c. X ray
10 Examination
a Description of lesions
b Location of lesions
c Work up
d Complete blood count
e Urinalysis
f Kahn
g Patch tests—if contact dermatitis
h Intradermal tests—if allergic dermatoses

DERMATOPHYTIDS

Williams originally demonstrated that certain eruptions on the hands were a mycotoxic manifestation of distant active fungus foci occurring on the feet The hand lesions result from dissemination of fungi or their products from foci on the feet and Williams called them dermatophytids Cultures of trichophyton are generally positive on the feet but negative on the hands It is thought that the fungi coming from the feet circulate in the blood and arrive in the allergic skin of the hands, where they are rapidly destroyed It is for this reason that fungi cannot be found in cultures from the hands Intradermal tests with trichophytin, monilia, and other fungi are usually positive either immediately, as with other protein reactions in allergic diseases, or delayed after twenty four hours as in the tuberculin type of sensitivity This indicates the presence of reagins against the proteins of the trichophyton fungus

Patch tests on these patients with trichophytin are also usually positive

Fungus infections on the hands can be classified into four distinct groups

1 Secondary to foot foci (dermatophytids)

2 Fungus hand infection possible from foot foci by external circuits

3 Primary hand infection with or without secondary foot involvement

4 A dermatitis on the hands due to an allergy to some food or other sensitivity in which the fungus infection on the foot acts as a predisposing factor inducing what amounts to a hyperallergy Several patients of this type were studied by Cleveland White and the author *

The following case reports will illustrate this type of sensitivity

Case Reports

Original fungus infection on foot—sensitivity to cottonseed oil Mrs R H age 30 housewife had an eruption of six years duration which appeared first on the plantar surface of the right foot and both hands Hyphae were recovered from the deep seated vesicles on the foot by the usual potassium hydroxide digestion method The eruption on the back of the fingers hands and wrists was a diffuse erythematous one with considerable edema on the flexural surfaces of the arms and forearms

Fungicidal preparations to the foot and soothing applications to the hands and flexures of the arms and forearms resulted in an improvement and the skin areas became clear Several weeks later an acute erythematous flare up reappeared on the hands and arms sides of the neck and legs This time however there was no discoverable activity on the feet We felt that this practically eliminated its being primarily a dermatophytid and that it must be a sensitization eruption A large series of intradermal tests was now performed with cottonseed strongly positive All other tests were negative

Cottonseed oil was eliminated from the diet and a clinical cure resulted with no recurrences Fungicidal preparations were used occasionally on the feet as a prophylactic measure and clinically and microscopically the fungus infection has completely disappeared

Further questioning revealed that as far as she could remember she

* Sensitization dermatoses of non fungous nature follow ng superfic al fungus infections (ringworm) of the extremit es *J.A.M.A* 98 524 5?7 February 13 1932

had placed cottonseed oil in cake before each attack It had been eaten many times before the original ringworm eruption and had produced no disturbance

Ringworm of the finger and nail, sensitivity to oatmeal A school girl age 12, had had a fungus infection of the right index finger for several weeks, with many small, thick roofed vesicles on the sides of the fingers Hyphae were found on potassium hydroxide preparations and eventually, on culture, Trichophyton interdigitale was grown The condition on the finger was somewhat slow in responding to therapy but, at the end of six weeks, was practically healed While the same preparation was being used, a discrete, patchy, erythematosquamous eruption appeared on all extremities

Because of previous experience in this type of case, a sensitization factor other than fungus was suspected Examination of the secondarily affected areas resulted negatively for fungi

Skin tests were all negative except to oatmeal which was positive

Inquiry into the diet disclosed that she had begun to eat oatmeal recently (fall of the year) and that she had eaten oatmeal every winter for many years Elimination of oatmeal from the diet resulted in a clinical cure

The fungus infection completely healed after several more weeks of local treatment

Fungus infection of foot, sensitivity to buckwheat A woman, age 21 college student, had had ringworm of the toes and plantar surface of her left foot for several months When first observed, the patient stated the condition was considerably better and improving, but she wanted advice as to a symmetrical, patchy eczematous eruption on the back of her hands, forearms, and thighs A few hyphae were found on the foot after considerable search but cultures were negative As the fungus infection was undoubtedly improving it was felt that the latter was due to some other cause

Skin tests with many substances showed only buckwheat to be strongly positive

Further questioning revealed that she had started eating buckwheat cakes just previous to the last eruption She had eaten them with impunity in other years. Elimination of buckwheat resulted in cure

Fungus infection on scalp, sensitivity to silk A high school girl age 15 had had an eruption on her face for one year and, according to her history, had received a great many roentgen treatments during that time

When first observed, the face was erythematous and edematous, the itching and burning was most intense The scalp had many patchy, dry, scaling areas, fitting into the clinical diagnosis of seborrheic dermatitis The important observations in her history were that there were marked exacerbations on her face, especially after attending dances, and that for a month previous to the onset of the face involvement she had had scaling areas in the scalp Skin tests were performed and she was found strongly sensitive to silk Discontinuance of wearing silk and then hyposensitizing to silk extract has produced a clinical cure, combined with local treatment to the scalp Cultures from the scalp scales yielded monilia, fungicidal therapy has clinically cleared that area

Although various fungi and bacteria are believed to cause scaling dermatoses in the scalp, and although there are some who do not believe in the infectious origin of many cases of so-called seborrheic dermatitis, we felt justified in calling the scalp manifestation a superficial fungus infection With extension to the face and eyelids and other structures the skin there became sensitive to silk At least the findings observations, and therapeutic response would indicate such a possible theory This case is cited because of its close association with other superficial fungus infections located elsewhere than on the extremities, where the first observations were made

In other patients tomato was found to be the offending food in 2, milk in 1, and chocolate in another In several patients, multiple sensitizations to several substances were elucidated

There is yet another phase of allergy that may enter into the 'dermatophytid problem A person may be sensitive to some protein, such as a food with which he comes in frequent contact, and yet remain free from symptoms Peshkin and Rost and Rackemann have found that about 10 per cent of children without symptoms of allergy are sensitive to one protein or another They are allergic but are held in equilibrium the term 'balanced allergic state has been advanced by Vaughan, meaning that the tissues are able to handle a given amount of the allergen without upsetting the allergic balance, and desensitization from eating small amounts of the allergen may be a factor in deferring symptoms An overdose, however, of the allergen will upset the equilibrium with an onset of symptoms One may be sensitive to two proteins, maintaining al

lergic balance while the contact is with only one but developing symptoms on exposure to both

In summary the fungus infections in these patients may likewise upset the allergic balance with the production of an allergic dermatosis affecting the hands face and various other parts of the body Also in some people who have fungus infections the skin is so altered that it becomes sensitive to certain foods and external irritants to which no previous clinical manifestations had ever occurred

URTICARIA

Urticaria and angioneurotic edema are often associated together because they have the same underlying pathology and because their etiology and pathology are analogous Erythema multiforme may possibly be a member of this group

Urticaria is a skin manifestation of hypersensitivity characterized by the occurrence of wheals surrounded by an erythematous halo and associated with an intense itching The lesions are multiple develop rapidly and regress quickly

Etiology

Urticaria may occur at any age and there is no relationship to sex. In the history we may uncover a tendency to some allergic disorder in the patient or in the family Contributing factors may be neurosis endocrine disturbances of thyroid or ovary fatigue exhaustion and acute or focal infections

The important causes of urticaria are to be found in hypersensitivities *to foods drugs serums inhalants and physical agents*

Of the foods eggs wheat cow s milk fish and strawberries are commonly responsible but in the author s experience acute urticaria is most often due to fresh fruits fresh vegetables nuts peas and beans fish pork chocolate tomatoes Coca Cola and other cola drinks The reaction may occur when the patient first partakes of the particular food or it may take place after ingestion of a food which has not been eaten for a long period

In the drug groups phenolphthalein and its compounds are frequent offenders. Aspirin quinine arsenicals bromides iodides acetanilid and antipyrine are common frequently used drugs that may produce urticaria The author has on several occasions seen a severe urticaria even from the use of ephedrine and barbiturates

Serum sickness occurs from five to twelve days after serum has been given to a nonallergic or normal individual who has not previously displayed any signs of sensitivity to the serum The resulting urticaria may be quite severe at times but is of temporary duration

Various substances may cause urticaria after inhalations The author demonstrated this as early as 1931 when he reported a severe urticaria involving the extremities which occurred in the grass pollinating season Tests were strongly positive to grass pollen and following a course of hyposensitization therapy the urticaria cleared and did not recur Silk and wool may also act as inhalants and are a common cause of urticaria Perfumes either by virtue of their essential oils or their content of coal tar derivatives may be the etiologic agent by inhalation as quoted by Dr Zakon

Physical agents such as exposure to light heat cold and mechanical irritation will cause disturbances in some individuals

Certain parasites such as trichophytons Sarcoptes hominis tape worm roundworm hookworm and pinworm are frequently found to be responsible for urticaria

Contact with clothing and dyes in clothing comprises a considerable proportion of the specific etiologies of urticaria Wool silk and cottonseed often act as contactants and patch tests with the suspected material will often reveal the active substance causing the hives Likewise cosmetics having cottonseed oil and lanolin as a base may be placed in this group

The role of bacteria in urticaria is still a much debated point The removal of *foci such as infected teeth and tonsils with improvement* in symptoms is a point which some maintain proves this contention

Symptoms

The primary and typical lesion is the wheal There may be only a few or several hundred of these present at the same time and they vary in size from a pin point wheal to one the size of the palm of the hand The lesions may coalesce to form oval or rounded irregular patches An erythematous flare may surround the wheal *Itching may* precede or accompany the eruption The wheals develop rapidly to reach their height and then disappear within a short time leaving no residual markings They may appear anywhere on the body It is thought by some that urticarial lesions may involve the mucous membranes of the stomach duodenum gall bladder and bile ducts

and give rise to various symptoms, depending upon the region involved

The acute type of urticaria is characterized by lesions which appear suddenly and remain for several minutes to a few days The chronic type is characterized by crops of hives, so that the skin is practically never entirely clear

Diagnosis

The history, the monomorphous character of the eruption, the sudden development of wheals and the rapid disappearance of the lesions make the diagnosis relatively simple In the differential diagnosis one must rule out the following conditions Erythema multiforme, erythema herpetiformis, erythema annulare, insect and animal bites with associated appearance of wheals contact dermatitis, such as poison ivy and primrose, and dermatographism

Treatment

Acute Stage The antihistaminic drugs afford the most relief in urticaria and angioneurotic edema These drugs should be used in their full dosage both orally and parenterally

Benadryl solution may be given intravenously in 3 to 5 cc amounts or hypodermically Histadyl solution, ½ to 1 cc, may be used subcutaneously as frequently as every four to six hours Decapryn minergic solution may be given subcutaneously in 1 or 2 cc amounts every twelve to twenty four hours

The oral use of ephedrine ⅜ grain, propadrine hydrochloride ⅜ grain to ¾ grain, and neosynephrin has been of some help In severe urticaria and angioneurotic edema, the combination of one of the antihistaminic drugs with ephedrine or propadrine hydrochloride gives excellent results

Calcium is of little or no value even though it is widely used orally, intramuscularly, or intravenously in the form of calcium gluconate, calcium chloride, calcium lactate, or calcium thiosulphate

When a suspected food has been eaten recently catharsis should be instituted at once Oatmeal, baking soda and starch baths are soothing to the itching skin Calamine lotion with 0 5 to 1 per cent phenol is widely used Other procedures that can be tried include spleen extract, 150 to 500 per cent intramuscularly, in doses of 0 5

to 1 0 cc, autohemotherapy, 10 to 20 cc, once to twice weekly, and sodium thiosulphate, 10 cc of a 10 per cent solution, intravenously Torantil (histamine) ace, orally, 5 to 10 units, one to three tablets three to six times a day, is of limited value It is derived from pork and must not be used in pork sensitive individuals

Skin tests are often disappointing during the acute state At times the food or drug that caused the eruption fails to give a positive reaction to the scratch or intradermal test Other times the skin is in such a hypersensitive state that any scratch or injection may produce erythema with wheals, and all tests appear positive Despite this drawback, skin tests should be carried out as they may be of some aid in the etiologic diagnosis

Chronic Type All the procedures mentioned under the acute type should be followed first The following must be investigated and ruled out Drugs, such as aspirin, phenolphthalein, salicylates, barbiturates, arsenicals, iodides, sulfas, and penicillin, inhalants, such as perfumes, cosmetics, feathers, bedding, wool, silk, and cottonseed, foci of infection, such as diseased teeth, tonsils, adenoids, and sinuses, and parasitic infestation, such as tapeworm, trichinosis, pinworm, and trichophyton Miscellaneous conditions, such as undulant fever, Hodgkin s disease, syphilis, and blood dyscrasias, may produce hives The endocrine group is probably responsible for the smallest percentage of cases

Urticaria may be due to menstruation, pregnancy, hypothyroidism, or the menopause The author has seen 3 patients with uterine fibroids who recovered completely from an intractable urticaria and angioneurotic edema following hysterectomy

Some urticarias must be considered as of psychogenic origin and may be attributed to emotional shock or unusual worries Physical allergies, due to cold, heat, light, or friction, also account for some urticarias Finally, some urticarias must be classified as of undetermined origin

Recently, various authors have referred to the use of histamine subcutaneously in small doses, histamine azo protein (Hapamine) subcutaneously, histamine ace in large doses by mouth or subcutaneously, daily subcutaneous injections of lobeline sulphate 05 to 15 Gm , and *ergotamine tartrate All of these drugs have been tried* but their value is doubtful

An intelligent patient can often help in detecting the offending food A food diary should be kept and each food eaten recorded, noting the correlation with urticaria At times it may be necessary to resort to elimination diets, such as those of Rowe (see Appendix) One need not follow Rowe s diets, but instead the patient can be given one food, such as milk, and then other foods can be added, one at a time, at intervals of three to five days Another method is the elimination of entire groups of foods for a period of ten to fourteen days For example, all fruits are eliminated, then all vegetables, meats, cereal groups, and fish, in succession

It can be readily seen that only after a thorough search and com plete examination using every possible laboratory procedure indi cated plus exhaustive skin tests can these troublesome symptoms be controlled

ANGIONEUROTIC EDEMA

This differs from urticaria in that it is characterized by large swell ings which involve the loose tissues, such as the mucous membranes of the lips, mouth, tongue, throat, and penis There is more of a tendency to burning than itching

Arthritic manifestations or pains referred to the epigastrium and gall bladder or meninges may accompany these swellings and they may be on the basis of internal urticarial edemas. Edema of the glottis is always alarming but, fortunately, it is rare

In the author's experience drugs, especially aspirin, quinine, phenolphthalein, amidopyrine, and fish, especially shrimp, lobster, and crabmeat are the most common causes of angioneurotic edema

In the treatment, epinephrine in oil, injected intramuscularly and repeated as necessary, should be given promptly All other drugs should be stopped at once Citrate of magnesia or magnesium sul phate should be given at once to remove the causative agent Skin tests should be done after symptoms have subsided Antihistaminic drugs given orally and parenterally give gratifying results

Locally, cold wet packs, consisting of liquor aluminum subacetate (Burow's solution), 1 teaspoonful to 1 pint of cold water (containing ice cubes), frequently applied, gives the most gratifying relief This medication also relieves the severe itching in urticarias

Chapter X

Drug Allergy

Drug allergy is caused by exposure to a drug to which an individual is hypersensitive Exposure may occur by ingestion, inhalation or by absorption from the mucous membranes of the skin and urogenital tract It differs from drug effects caused by pharmacologic action or toxic effects in that only minute amounts are necessary to produce symptoms so minute, in fact that no effect is produced on nonallergic people

The mechanism in drug allergy is similar to that in serum allergy in many respects and as in serum allergy, there are several types One type is the natural, hereditary, or atopic variety

The reaction produced in atopic drug allergy is usually immediate, such as asthma or hay fever, and may be severe or even fatal It resembles the reaction observed in patients atopically sensitive to horse serum

In both instances drug allergy and horse sensitivity, symptoms are produced by the transmission through heredity, of a sensitive shock organ, so that subsequent exposure to the specific drug or horse serum produces allergic reactions They differ, however in one main respect Skin tests and passive transfer tests are positive in the horse *serum sensitive* patient, whereas in the drug sensitive individual these tests are usually negative The patient who develops a severe asthmatic attack from the ingestion of a small quantity of aspirin or barbiturate is atopically sensitive but will not show a positive skin test The drug is not a protein but it is thought that a sensitivity is

produced due to a combination of the drug with the body proteins Landsteiner has termed this new protein combination a hapten protein and it has been shown that these hapten proteins act as antigens

The second type of drug allergy is the nonatopic, or acquired form, which resembles serum sickness in that there is a definite incubation period before the onset of symptoms following exposure to the drug However, there is an absence of positive skin tests A blood eosinophilia may be present but neither reagins nor antibodies are demonstrable.

SYMPTOMATOLOGY AND DIAGNOSIS

In the acquired or nonatopic type of drug allergy an incubation period of a few hours to twenty four hours intervenes between the administration of the drug and the onset of symptoms The most common type of eruption produced by drugs is urticaria and angioneurotic edema Aspirin, barbiturates, salicylates, phenolphthalein, atropine, morphine and its derivatives, and codein may produce this type of eruption

The eczematous producing drugs are quinine, arsenicals, ephedrine, and procaine

The arsenicals, heavy metals, sulfonamides, and nirvanol cause a scaly erythematous eruption Purpura is caused by arsenicals, barbiturates, iodides, sedormid, and sulfonamides Lesions which are acneform are caused by bromides and iodides

Fixed and circumscribed skin eruptions which may be erythematous, bullous or pigmented are produced by phenolphthalein, arsphenamine, antipyrine, phenacetin heavy metals, barbiturates and sulfonamides As a matter of fact, the skin manifestation of a drug allergy can be in any form and mimic any disease

Granulocytopenia results from allergy to amidopyrine and dinitrophenol Fever, swelling of joints, enlarged lymph nodes and an eosinophilia may accompany the eruption

Many of these drugs especially phenolphthalein, are found in more than one hundred proprietary medicines *

Amidopyrine and dinitrophenol are also frequently found in many proprietary preparations and may thus not be easily recognized unless looked for It is also common that a patient who is sensitive to

* Belote and Whitney *Arch Derm & Syph* 36 1937

one drug may become sensitive to another drug unrelated to it The sulfonamide group of drugs produces photosensitization as well and patients treated with these drugs should be instructed to avoid direct sunl ght for three or four days after taking them The same or related drug will produce the same type of lesion on repeated use

The diagnosis is simple if one will keep in mind the fact that one may become sensitive to almost any drug in common use The clin ical picture a history of taking some drug preparation followed by an interval before the appearance of symptoms and the improvement which follows withdrawal of the medication are typical of this form of allergy On re exposure to the drug the identical symptoms will recur

Unfortunately scratch and intradermal skin tests are negative but patch tests may be positive in quinine sensitivity The latter may cause a contact dermatitis when it is directly applied to the skin and an eczematous eruption following its internal use

PENICILLIN

Reactions to penicillin are quite common and for some unknown reason men are affected more often than women According to a recent study by Peck Seigal Glick and Kurtin * the incidence among 130 patients is 34 2 per cent in men and 8 3 per cent in women

The reactions encountered are of the urticaria serum sickness like type with joint pains and fever in some instances which occur after a definite incubation period These allergic reactions occur in some 75 per cent of patients who react to penicillin while the erythemato-vesicular trichophytid type occurs in about 25 per cent Because of the time needed for development of the newly induced sensitivity the reaction was called the delayed type by Kalodny and Denloff Quite frequently it manifests itself several days after termination of treat ment with the drug In some patients this interval may be as long as three weeks Severer reactions with angioneurotic edema hyper pyrexia pulmonary edema and asthma have occurred

Some reactions which occur on second or subsequent administra tion of penicillin may be of the accelerated type with a short or no incubation period This acceleration is similar to what may occur on readministration of serum or sulfonamide drugs

* *J.A.M.A* Oct 1948

The usual incubation period is seven to twelve days although it may vary from two to eighty days

The eruption varies from a slightly patchy erythema of a transient character to pronounced generalized urticaria of considerable severity Macular erythemas not urticarial in type are common In some patients the eruption may be limited to the buttocks and thighs

Reactions may occur following the intramuscular injection of the drug or following the oral ingestion of tablets of penicillin Urticaria has followed bronchoscopic instillation and aerosal therapy Usually the eruption clears within several days, although one patient of mine continued to have generalized urticaria and joint effusion in both hands and knees for a period of three months

Peck, et al , skin tested 406 adults and 93 children with penicillin and trichophytin Of the adults, 276 had never previously been given penicillin, and of the children, 65 had had no previous penicillin treatment

Tests were performed by the intradermal method, with readings being made at either fifteen minutes for the immediate response or forty eight hours for the delayed reaction using the standard allergic test dose of 0 01 to 0 02 cc of the commercial penicillin

For the delayed intradermal reaction, 2000 units or about 1 2 mg of crystalline penicillin in 0 1 cc of isotonic solution of sodium chloride was employed The trichophytin preparation employed was freshly made from Trichophyton mentagrophytes according to a method described previously by the authors the test being performed in the standard manner with 1 30 dilution in 0 1 cc of isotonic solution of sodium chloride, with readings made at forty eight hours and again on occasion at three to five days

The authors agree with Welch and Rostenberg that the delayed reaction to the intradermal injection of penicillin is the most important test of penicillin sensitivity

The test, similar to that seen in trichophytin sensitivity, is characterized by an area of erythema, often rather vivid usually associated with edema or infiltration and sufficiently prominent in induration to give the resulting lesion a plaque like appearance, the reaction area often being 1 0 cm in diameter but sometimes reaching three times this size and studded with small papules and occasionally vesicles An occasional central necrosis may be observed The reaction may reach

its height three to five days after testing and may persist a week or more, gradually disappearing, being associated with local pruritus and scaling In one of my patients, evidence of the test could be seen three months later

Sensitivity may be very exquisite, a positive reaction having been seen in a patient with 5 units (0 0025 mg crystalline penicillin) The authors found the patch test of doubtful value as an index to penicillin allergy as applied in ointment form with 1000 to 2000 units of penicillin per gram in hydros wool fat base

Reactions to immediate tests were also negative, although the same solutions gave positive reactions of the delayed type

While a positive reaction to a penicillin test may be helpful in confirming a diagnosis of this type of allergy, a negative reaction does not exclude it Since a reaction to penicillin may be positive in more than one third of such patients the test is worth doing in an effort to prove that an eruption is caused by penicillin, the test thus being of practical value when several drugs are being given simultaneously The incidence of the delayed type of positive reaction to the penicillin test in this group of patients allowing to 40 per cent, was far greater in the group that had never received penicillin The so-called spontaneous reaction occurred in 5 per cent of such patients routinely tested

Of 98 patients who had received penicillin without reaction not one reacted positively to the cutaneous test Of the 130 patients receiving penicillin who were tested, 17 had a positive reaction of this type, an incidence of 13 4 per cent

A second type of penicillin sensitivity may be described as a reaction with erythematovesicular eruption of the trichophytid form It may exist in a latent and in an active stage, the former being demonstrated by no clinical signs but simply by the presence of a delayed forty eight hour positive cutaneous test in a patient who had never been given penicillin

The active stage is the characteristic erythematopapulovesicular eruption which tends to localize primarily on the hands and feet and in the groins

It may become generalized or start on the trunk, but is likely to be more intense on the extremities It may progress to a severe, vesiculobullous reaction which may become pustular The reaction may

be accompanied by general desquamation and, if acute, may be an exfoliative dermatitis

The positive reaction to the trichophytin test may be taken as an index of resisting sensitivity to this fungus infection The relation of the positive penicillin reaction to the trichophytin reaction is therefore of great interest

The tests carried out simultaneously in patients who have not had *penicillin treatment showed positive reactions in* 92 (38 3 per cent) Among the 15 penicillin positive patients there were 9 who were also trichophytin positive, or an incidence of 6 per cent, almost twice the incidence among the penicillin negative patients On the other hand 6 patients with this form of penicillin sensitivity were trichophytin negative One must conclude that these patients were sensitized in some other manner or that in some persons cutaneous infection with a fungus may not induce a positive trichophytin reaction, or that the reaction humorally is only temporary or below the threshold of elicitation The percentage of patients sensitive to penicillin among the trichophytin positive patients was 9 7 as against 3 2 among the trichophytin negative patients This incidence offers evidence of the role of fungus infection in producing latent penicillin sensitivity It is important to test with penicillin all patients for whom treatment with the drug is planned

A negative reaction does not preclude the possible development of the induced form of urticarial sensitivity

PENICILLIN DESENSITIZATION

Oral Method Crystalline penicillin is administered dropwise in a solution containing 5000 units per cc In this way small amounts less than 1000 units a day, can be given initially The concentration is increased to 20 000 units per cc After three weeks tablets of crystalline potassium penicillin are given, at first 100 000 units a day later as much as 500 000 units daily Should reactions occur, the dose should be decreased and continued on a level that does not result in reactions This regime should be followed until the skin test to penicillin shows negative

Therapeutic Desensitization When the need for penicillin is urgent, a modification of the usual technic is suggested employing so-called therapeutic desensitization Such patients should be under

close observation, preferably in a hospital After an initial provocative dose of from 1000 to 5000 units depending on the degree of previously observed sensitivity penicillin might be given every three hours in the same dose for the first twenty four hours Evidences of a reaction should be looked for after each injection and before the *next dose is given On each day following the dose can be increased* until an adequate therapeutic dose is obtained It is likely that the tendency to lose penicillin sensitivity spontaneously which has already been frequently noted among patients with type 1 sensitivity can be hastened with judicious employment of this schedule

Injection	*Number of Units*
1	200
2	400
3	800
4	1 200
5	1 600
6	2 000
7	2 500
8	3 000
9	5 000
10	10 000
11	15 000
12	20 000

The interval between injections may be two to three days When more rapid desensitization is necessary daily injections may be given If the patient is extremely sensitive the initial dose may be as low as 50 units *and subsequent increase in dosage much more cautiously* tried Should a local reaction or a rise in temperature occur after the increase in dosage the subsequent dose is that which elicited no reaction and increasements should be smaller *

In the contact type of dermatitis due to penicillin sensitivity, desensitization is as follows Starting with 05 cc of a solution of 10 units per cc three times weekly the dosage is increased as in pollen sensitivity After 1 cc *is given start with 100 units per cc* then 1000 10 000 and 100 000 units per cc

* Peck Samuel M Siegel Shaffard Click Arthur W Kurtin Abner Penicillin sensitivity *J.A.M.A* p 631 Oct 30 1948

SKIN SENSITIVITY TO STREPTOMYCIN

There have been several reports in the literature of the occurrence of contact dermatitis following frequent handling of streptomycin by physicians and nurses

The sensitivity is apparently due to frequent contact with solutions of the drug Past or present allergy or penicillin sensitivity has no effect on the development of skin sensitivity to streptomycin

Simon describes a method of patch testing large groups of personnel who handle this drug to determine positive reactions A solution of 1 per cent streptomycin calcium chloride (or dihydrostreptomycin sulfate) was prepared in distilled water Strips of filter paper (1 cm in width) were hung to dry in an air circulating oven at about 40° C The dried strips were cut into squares 1 × 1 cm Two squares were applied to a strip of adhesive tape 1 × 3 inches and then pieces of crinoline were applied to the adhesive face Each patch was then trimmed and individually packaged in a glassine envelope The patches were not sterilized In the case of the streptomycin patches filter paper squares were similarly prepared saturated with streptomycin nutrient broth One such square was included on each adhesive strip as a control The patches were applied to the skin of the back over the scapula area after cleansing with acetone It was left in situ for forty eight hours

Simon tested 248 persons of whom 182 were nurses and 160 had handled the drug or washed syringes after injection Only 8 positive reactions were obtained of which 4 were nurses with the typical eruption on their hands and fingers The incidence in this group is small only 2½ per cent developing contact dermatitis who actually were in contact with the drug while a similar number showed a positive patch test who did not develop any symptoms As prophylaxis Simon lists the following measures

1 Rubber gloves are to be worn whenever syringes containing or having contained streptomycin are handled Gloves so used are to be washed with tincture of green soap before being discarded and are not to be worn again before sterilization by boiling or autoclaving

2 Streptomycin syringes after use are to be taken apart and placed in a receptacle with running warm water for fifteen minutes

3 All personnel who either administer streptomycin or handle the syringes which contained it should be patch tested with 1 per cent streptomycin at least every two months

This last suggestion however, is open to serious criticism since it has been shown that frequent patch testing with a potent skin sensitizer may actually result in sensitization of the skin, like poison ivy extract, which has been shown to cause contact dermatitis after frequent patch testing

Treatment The application of 2 per cent pyribenzamine daily to the lesions and the administration of 50 mg of pyribenzamine internally four times a day resulted in relief in a short period of time Dermolate was used in place of soap

Biological Products as Antigen

Various biologicals, such as insulin, liver extract, tissue extract, and pituitrin, may be the cause of serious allergic disturbances

Hypersensitivity to Liver Extract Injections of liver extract may produce allergic symptoms in patients who show a natural or atopic *sensitivity to the liver itself, or a sensitivity to the animal from which* the liver was obtained

The majority of reactions to liver extract are due to an allergy to the liver tissue itself (organ specific allergy) and only in a few instances has a species specific allergy, i e, an allergy to the animal muscle, and serum from which the liver extract was obtained been proven This fact is of the utmost importance in treatment since, in an allergic reaction of the species specific type, i e, to pork muscle, serum, and liver for example, all that would be necessary to continue treatment would be to change to a beef extract On the other hand, if the sensitivity exists to the protein of the liver itself (organ specific allergy), treatment with liver extract must be stopped at once because the patient will not tolerate this medication regardless of the source

Many types of reactions are observed following treatment with liver extract A local Arthus type of reaction may occur following one or repeated injections with the production of large inflammatory swellings with edema Systemic reactions consist of urticaria, asthma, severe gastrointestinal disturbances and shock reactions, with collapse of anaphylactic nature Intradermal, scratch, and passive transfer tests are positive in these patients using the liver extract

preparations in testing Severe gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhea, may follow the oral ingestion of liver extract when the patient is atopically sensitive to beef, pork, or lamb

It has also been observed that patients who have pernicious anemia and become hypersensitive to liver extract do not obtain the anti anemic response to the liver therapy This same observation has been noted in diabetic patients who become sensitized to insulin Cannon explains this interference on the basis of localization of the liver extract or insulin in the tissues with a consequent lack of absorption

In the treatment, injections must be stopped and in the organ specific type (sensitivity to the liver protein) an attempt is made to hyposensitize the patient, starting with a very dilute solution of the liver extract, of 1 1000,000, or 1 100 000 dilution, gradually increasing the amount and the concentration until more concentrated extracts can be given without the production of reactions Results are usually not promising since such large amounts must be given in pernicious anemia in order to obtain a good therapeutic response In the few instances that species specific reactions occur (allergy to beef, pork, or lamb muscle) all that is required is to change from beef to lamb or pork, or vice versa

Insulin Sensitivity Many insulin sensitivities are due to the use of the protein protamine and beef globin, which may form a new compound with the native protein insulin and act as a hapten Some patients may develop a hypersensitivity to the crystalline insulin itself, demonstrating the production of an allergy to the body's own native protein To illustrate this type of sensitivity, the author quotes the following case report

Mrs F M, age 52 was a moderately severe diabetic controlled with 30 units of protamine zinc insulin and 45 units of regular insulin per day The insulin dosage was gradually reduced, and after a few months was completely stopped Following an interval of six months, regular insulin was again resumed, and within an hour following the first injection a severe urticaria angioneurotic edema involving the face, eyes and lips, and asthma followed Further insulin injections were stopped and the symptoms were controlled with the use of epinephrine and ephedrine

The patient was referred for tests to determine whether an allergy existed to insulin, to beef, or pork Tests to beef, pork, and protamine

were negative whereas a scratch test to crystalline insulin produced a large reaction with pseudopods and a large red areola

Crystalline insulin was diluted to one part to a million and hyposensitization was started with 0 1 cc and increased by 0 1 cc every three days until 1 cc. was tolerated without producing very large local reactions The same procedure was followed using 1 100 000 dilution then 1 50 000 1 10 000 1 1000 1 100 1 10 and finally the pure undiluted crystalline insulin This patient was finally able to take 15 units of protamine zinc insulin plus 10 units of regular insulin three times a day without further allerg c reactions

Hyposensitization to insulin is possible but the procedure is slow and painstaking It requires considerable time but should be undertaken in these patients since an allergy to insulin in diabetics results in a lack of absorption and in interference with therapeutic response

Likewise tissue extract and pituitrin may cause allergic reactions when injected over a period of time then stopped for a period and then resumed after an interval Many allergic reactions such as urticaria angioneurotic edema and asthma may follow the first injection of these biologicals

When these symptoms occur the use of these biologicals must be stopped at once

TREATMENT

The important principle in the treatment of drug allergy is to stop the drug Allergic patients in particular should not take drugs unless ordered by the physician In the patient with chronic urticaria all cathartic mixtures which may contain phenolphthalein and all sedatives containing bromides or phenobarbital should be promptly stopped

The antihistaminic drugs should be used in large enough doses to control the symptoms Pyribenzamine or benadryl in 50 mg doses every two to three hours may be given In a recent patient with severe angioneurotic edema urticaria and edema into several joint spaces a dosage of 700 mg pyribenzamine a day was required to control symptoms

Benadryl intravenously 3 to 5 cc containing 30 to 50 mg of the drug often results in spectacular relief

Histadyl (thenylpyramine hydrochloride Lilly) containing 20 mg

per cc can also be used intravenously starting with ½ cc (10 mg histadyl) and increased to 1 or 2 cc cautiously

Procaine hydrochloride intravenously has been advocated recently in the treatment of reactions to penicillin and serum sickness One gram of procaine hydrochloride in 500 cc of physiologic saline is given by the intravenous drip slowly *The solution should take at* least three hours to be given

It should be emphasized that procaine hydrochloride may cause toxic effects and is a well known sensitizer Allergic shock has fol lowed its use There are no known tests to determine sensitivity and its routine use in serum sickness and penicillin reactions is not suffi ciently well founded

It is necessary to administer preparations extracted from liver to patients with pernicious anemia and macrocytic anemia such as sprue syndrome and because manifestations of allergy develop in a small number of patients after the use of these preparations it is advisable to administer antihistaminic drugs to these individuals to enable them to tolerate therapeutic doses of liver extract Checking the cutaneous sensitivity of patients to liver extract before treatment with the extract is started seems impractical because of the infre quency with which systemic reactions to parenterally administered liver extracts occur and because of the high incidence of cutaneous sensitivity in individuals who exhibit no allergic manifestations

Such generalized reactions almost invariably occur only after prolonged administration of liver extract or when the treatment is stopped for some time and then started again after an interval The reactions most commonly observed are urticaria angioneurotic edema and asthma Less frequently anaphylactic shock atopic der matitis and diarrhea may occur

Treatment of Reactions

In hyposensitizing to liver extract the initial dose should be of high dilution Starting with a 1 1000 dilution 0 1 cc of diluted liver extract is injected subcutaneously This dose is increased by 0 1 cc. every half hour if no local or general reactions occur until 0 7 cc is given Then 0 1 cc of a 1 10 dilution is injected intramuscularly and increased by 0 1 cc every half hour until 0 7 cc is given.

If no reactions occur, the undiluted concentrated liver extract is given 0 1 cc intramuscularly every half hour and increased by 05 cc until 0 5 cc is given

Benadryl 50 mg, pyribenzamine 50 mg, Neo antergen 50 mg, or any of the antihistaminic drugs are given three times a day after meals during the entire period of hyposensitization

Desensitization to Liver Extract*

First day	50 mg of benadryl by mouth three times a day after meals
Second day	50 mg of benadryl by mouth three times a day after meals
Third day	(Epinephrine and syringe should be made available)
8 00 A M	100 mg of benadryl by mouth
9 00 A M	0 1 cc of 1 100 dilution of concentrated liver extract injected subcutaneously
9 30 A M	0 2 cc of 1 100 dilution of concentrated liver extract injected subcutaneously
10 00 A M	0 4 cc of 1 100 dilution of concentrated liver extract injected subcutaneously
10 30 A M	0 7 cc of 1 100 dilution of concentrated liver extract injected subcutaneously
11 00 A M	0 1 cc of 1 10 dilution of concentrated liver extract injected subcutaneously
11 30 A M	0 2 cc of 1 10 dilution of concentrated liver extract injected subcutaneously
12 00 M	0 4 cc of 1 10 dilution of concentrated liver extract injected subcutaneously 50 mg of benadryl by mouth
12 30 P M	0 7 cc of 1 10 dilution of concentrated liver extract injected subcutaneously
1 00 P M	0 1 cc of undiluted concentrated liver extract injected intramuscularly
1 30 P M	0 15 cc of undiluted concentrated liver extract injected intramuscularly
2 00 P M	0 25 cc of undiluted concentrated liver extract injected intramuscularly
2 30 P M	0 4 cc of undiluted concentrated liver extract injected intramuscularly

* Carryer Haddon M and Koelsche Giles A Use of antihistaminic drugs in treating patients allergic to liver extract *J Allergy* 19 376 383 1948

3 00 P M	0 5 cc of undiluted concentrated liver extract injected intramuscularly
6 00 P M	50 mg of benadryl by mouth
ourth day	50 mg of benadryl by mouth three times a day after meals 0 5 cc of undiluted concentrated liver extract injected intramuscularly one hour following first dose of benadryl
ifth day	Same as on fourth day
ixth day	50 mg of benadryl by mouth three times a day after meals
eventh day	Same as on fourth day
ighth day	50 mg of benadryl by mouth three times a day after meals
Ninth day	Same as on fourth day
Tenth day	50 mg of benadryl by mouth three times a day after meals
leventh day	50 mg of benadryl by mouth three times a day after meals
Twelfth day	Same as on fourth day
ourteenth day	50 mg of benadryl by mouth three times a day after meals
ifteenth day	Same as on fourth day
eventeenth day	50 mg of benadryl by mouth three times a day after meals
ighteenth day	Same as on fourth day thereafter weekly as on fourth day use of benadryl on the day preceding the injection of liver extract is eliminated

Chapter XI

Miscellaneous Allergic Conditions

GASTROINTESTINAL ALLERGY

Historical

Hyde Salter, in 1868, noted gastrointestinal symptoms in an asthmatic patient who was milk sensitive The first recorded case of buckwheat sensitization by Smith in 1909 also had gastrointestinal symptoms Duke, Eyermann, Alexander, Vaughan, and Rowe repeatedly demonstrated the important effect of food allergy on the gastrointestinal tract

Etiology

The exact incidence of gastrointestinal allergy is not known The symptoms may not be recognized as being allergic and may accompany other manifestations of allergy The hereditary factor is important and a positive family history is frequently obtained Other allergic diseases such as eczema, migraine, hay fever, or asthma may be present

Diagnosis

When gastrointestinal symptoms accompany asthma, hay fever, eczema, or other allergic disorders, foods or drugs should be suspected as the cause

The patient with abdominal symptoms or gastrointestinal complaints, showing no other allergic disorders, should be suspected of

being food sensitive after organic disease has been ruled out by the usual diagnostic procedures Intolerance to indigestible foods like onions, cabbage, pickles, radishes, and cauliflower must be differentiated from food allergy, although these foods may cause urticaria and allergic symptoms in the gastrointestinal tract Flatulence heart burn, belching, and vomiting may likewise result from fat or sugar intolerance as seen in gall bladder disease and diarrheas from fermentation The diagnosis then is based on a hereditary history of other allergic diseases and a history of a dislike for the food or foods

Positive tests to foods may be obtained Where skin tests are negative, clinical trial with removal of the food or foods should show relief of symptoms while the addition of the same foods is followed by return of the symptoms

TREATMENT

The complete elimination of the foods from the diet is essential in the treatment of these patients When severe abdominal pain is present epinephrine may be used with excellent results for relief of symptoms The various antihistaminic drugs are also helpful in patients with diarrhea When foods are completely eliminated the symptoms disappear within one to two weeks

SYMPTOMS

The ingestion of foods may cause various symptoms in the gastrointestinal tract which may simulate acute food poisoning, cholecystitis or cholelithiasis gastritis gastric ulcer and colitis The reaction is due to direct contact of the protein of the food upon the mucosa, or as a part of a general reaction after the protein has been absorbed

The recognition of the relationship between the food eaten and the symptoms following is quite simple when an uncommon food such as crab, shrimp strawberries or lobster is eaten However, it is the common foods eaten daily, such as eggs milk, wheat and chocolate, that are responsible for symptoms of gastrointestinal allergy and usually these foods are not suspected as the causative agents

Mouth and Lips Swelling of the lips and tongue may follow the ingestion of certain foods in sensitive patients Eggs, milk, sea foods and strawberries are frequent offenders

Recurrent canker sores have occurred following the eating of cab

bage, wheat, and chocolate When the offending food is eliminated, complete relief has followed Stomatitis from sensitization to dental plates has been reported by Rattner

Esophagus Edema of the glottis, burning, retching, and sour eructations have occurred in food allergy

Stomach Since it has been demonstrated that canker sores can be caused by allergy to foods it may be possible that ulcerations in the stomach and duodenum may likewise follow food sensitivity Ivy and Shapiro have reported the production of gastric ulcers in rabbits and dogs by first sensitizing the animals to a foreign protein and later injecting a small quantity of the same protein into the gastric mucosa In a small series of 32 unselected cases of duodenal ulcer studied by Kern and Stewart, 40 per cent gave a personal history of other allergic conditions, 60 per cent gave positive skin tests to food proteins, 25 per cent gave suspicious reactions, and only 15 per cent gave negative reactions

Those patients who showed positive skin tests to foods were relieved of symptoms after eliminating them and suffered a return of symptoms after eating the specific foods It is true that this series of patients is too small for definite conclusions yet in the author s experience food hypersensitiveness may be an etiologic factor in a small but appreciable percentage of cases of gastric and duodenal ulcer When ulcer symptoms are aggravated on a milk and cream diet a sensitivity to milk should be suspected and this possibility investigated Should skin tests to the milk proteins be found negative, its elimination from the diet for a few days may be conclusive evidence, if symptoms are relieved

Cyclic vomiting and pylorospasm in infants have been reported due to egg cereals and milk sensitivity Allergic sensitivity may have occurred from the mother in early intra uterine life, and after birth a dose of the specific allergen results in spasm and edema around the pylorus with resulting symptoms

Diarrhea spastic colitis, and mucous colitis have been traced to hypersensitivity to foods Itching in the rectum and perianal regions may be caused by food allergies and the author has found wheat, orange, and coffee as causative factors in some patients

During the pollen seasons, some hay fever patients complain of rectal and perianal itching accompanying hay fever symptoms

Cholelithiasis, cholecystitis, appendicitis, and intestinal obstruction may simulate severe reactions from food allergies in the gastrointestinal tract, and a differential diagnosis may at times be difficult unless this possibility is kept in mind If skin tests to food are negative, elimination diets may be helpful in finding the offending food

ALLERGIC PURPURAS

The Schoenlein and Henoch types of purpura are characterized chiefly by increased capillary permeability *with normal platelet* counts and normal bleeding time and clot retraction

Anaphylactoid purpura is more descriptive of this group since various foods and drugs have been reported as causative agents

Hemorrhages from the nose, vagina, rectum, and gastrointestinal tract may occur, as well as petechial hemorrhages into the skin Wheat, eggs milk potato, cabbage, onions, nuts, and fish have been reported to cause this reaction

Thrombocytopenic purpura has followed the use of drugs orally, or following intravenous injection Quinine, the sulfa group, se dormid, ergot, neoarsphenamine, urotropin, bismuth phenobarbital, and coal tar drugs may cause a pronounced drop in the platelets prolonged bleeding time, and poor clot retraction in drug sensitive patients

The author has studied several patients with nonthrombocytopenic purpura of the Henoch type, all occurring in *young females* between the ages of 16 and 20 years in whom foods were the etiologic factor Wheat and fish proteins were responsible in this group and following their removal from the diet complete recovery took place *Passive transfer tests on nonallergic individuals resulted in positive* tests to these substances

ALLERGY OF THE EYE

Any tissue of the eyeball or its covering may be involved in *allergic* reactions A high incidence of allergy in certain ocular diseases has been observed

Hay fever conjunctivitis simplex, vernal conjunctivitis scintillating scotomas, migraine blepharitis angioneurotic edema of *the lids* and eczema of the lids are the most common allergic conditions in which the eyes may be affected

Offending allergens include dust, smoke, pollens, novocaine, butyn, cocaine, and pontocaine, astringents such as zinc and atro pine, ointments and bland lotions such as boric acid solution of from 3 to 10 per cent may cause allergic eye conditions Normal saline solutions never cause irritation even in persons allergic to other lotions Bowen considers vernal conjunctivitis as analogous to con tact dermatitis and he finds botanical and environmental factors important etiologically Food sensitivity does not play a factor in this type The nonvernal type may be due to cosmetics, drugs, bacteria, foods pollens, fungi and environmental factors according to this author

Inhalant factors such as dust, pollens, feathers, orris root, smoke, and silk are of greater importance etiologically than foods Cosmetics, local anesthetics, lotions, drugs, and soap may act as contactant fac tors Perfume, cologne, and face powders are also responsible for blepharitis and conjunctivitis in some cases

Patch tests are usually negative, but intradermal tests to inhalants and foods may be positive In the treatment all local medication should be stopped and a normal saline solution used locally as an eye wash Epinephrine and ephedrine locally or by injection usually aggravates the condition because of the vasodilation that follows the temporary vasoconstriction produced by these drugs Ocular rest and wearing dark glasses to protect the eyes from light are helpful If foods are found positive, they should be eliminated from the diet and hyposensitization with inhalant factors such as dust, silk, and orris root should be undertaken if these substances are etiologic agents

In a recent article by Benjamin R Gutman M D Mary Jane Fowler, M D , Robert E Miller, M D , Robert G Taub M D , and the author * 30 patients were studied who had an allergic manifesta tion of the eye proper and its surrounding tissues The symptoms and findings encountered included lachrymation, photophobia, itch ing burning pain blurring of vision conjunctivitis superficial punctate keratitis corneal ulceration, chorioretinitis, macular hemor

* Taub S J *et al* Allergic manifestations of the eye and surrounding structures *Am Pract* 3 664 671 1949

rhage, ciliary injection swelling of the lids and dermatitis of the eyelids

The incidence of ophthalmologic conditions in this series is as follows

Ophthalmologic diagnosis	*Incidence in series*	*Percentage of patients*
Conjunctivitis	28	93
Vogt Koyanagi syndrome	1	3 3
Dermatitis about the eyes	7	23 0
Superficial punctate keratitis	19	63 0
Angioneurotic edema	1	3 3
Pseudomembranous keratoconjunctivitis	1	3 3
Iritis	1	3 3

Eosinophils were present in all eye smears and scrapings in a greater or less degree By direct counting counts of from 450 to 500 per cu mm were encountered (Normal for this method is from 150 to 250 per cu mm)

The following symptoms were presented

Major Symptoms	*Number times found*	*Percentage of patients*
Blurring of vision	5	17
Swelling of eyelids	11	38
Eruption about lids	4	14
Burning and itching	13	45
Photophobia	16	55
Pain	5	17
Lachrymation	10	33
Redness of the eyeball	28	93

The antihistaminics possess but slight effectiveness in treatment of these eye conditions because of their fleeting action and because of the distressing side reactions Local antihistaminics such as *An tistine* 0 5 per cent may cause acquired sensitization Cortisone, used locally in the eyes is highly beneficial and affords symptomatic relief It is given in the following prescription

Cortisone 2 0
Normal salt sol 8 0
Sig 2 drops on eyes every hour for 6 or 8 doses

One of the author's patients with vernal conjunctivitis was found sensitive to silk protein She was the owner of a dress shop and noted that eye symptoms were always increased when she was in the shop handling silk dresses While on a vacation the eye symptoms improved only to recur on returning to the shop Intradermal tests were positive to silk only and patch tests to silk and cosmetics were negative She was advised not to handle silk dresses and to wear only cotton, rayon, or wool Hyposensitization to silk protein extract was carried out and no further eye symptoms appeared Likewise other patients have been observed with severe conjunctivitis appearing only during *the pollen season without nasal symptoms of hay fever* Grasses and the ragweed group of pollens were found responsible, and following hyposensitization with the offending pollens complete relief took place with no recurrence the following season, when perennial treatment was instituted

Allergy may not be the cause of all ocular diseases of this type, yet when infection has been ruled out, a thorough allergic study may elicit the etiologic factor and result in symptomatic and physical improvement

MIGRAINE AND ALLERGIC HEADACHE

That headaches of the migraine type may be allergic was first demonstrated conclusively by Vaughan in 1927, who found positive skin reactions to certain foods, relief of symptoms following avoidance of these foods and subsequent induction of symptoms after eating them

It is thought that the basic change is an edema of the meninges due to sensitivity to foods, although inhalant factors have also been shown to play a factor in the etiology Allergy is probably not responsible for all migraine headaches although it is responsible for the majority of cases Where there is a regular periodicity of symptoms occurring with the catamenia, it seems probable that there is an associated endocrine disturbance Thyroid dysfunction and gonadal pituitary types of endocrine dyscrasia may be responsible for some of these cases and an allergic factor may be associated with this type as well Fatigue, constipation, infection and emotional excitement may precipitate an attack of migraine by acting as nonspecific activating factors

Skin tests to foods unfortunately, are not reliable since negative

reactions may occur to a food to which the patient is actually sensitive Many of the foods responsible for attacks of migraine may show only borderline or suspicious reactions All foods reacting positively and in a borderline manner should be eliminated from the diet After the patient is relieved, one food after another may be added to the diet until symptoms are reproduced

It is important to keep a food diary, only eating those foods found completely negative on skin tests and recording each attack of migraine as it develops After a number of such episodes have occurred careful study of the diary will sometimes show that certain foods have been eaten only within the twenty four hours preceding an attack It will then be simple to eliminate each food, one at a time, for one week and then reintroduce it on an empty stomach If the particular food eaten should result in an attack within one to twenty four hours, the etiologic food or foods can be determined with certainty

If all intradermal skin tests are negative, a clinical sensitivity to foods may still be present, and when elimination of all positive reacting foods is not followed by relief one must resort to elimination diets as suggested by Rowe and clinical trial of one food at a time In testing these patients, it is important to test with potent extracts, using the intradermal technic, and to note all doubtful or suspicious reactions or delayed reactions

SYMPTOMATOLOGY

Attacks of hemicrania are usually preceded by an aura of prodromal symptoms such as vertigo hunger, diarrhea, nausea, abdominal pain, changes in sensation of smell or taste, and various other vasomotor or sensory disturbances These symptoms may precede the attack of headache for from one to three hours or they may be entirely absent The headache may begin over one eye or be limited to one half of the head (hemicrania) Actual pain on movement of the eyeballs and local tenderness of the scalp may be present Often the pain becomes generalized to include the entire head

During the height of the pain, nausea and vomiting usually occur Tinnitus aurium, vertigo, and visual disturbances frequently occur during the attack Scintillating scotomas (flashes of light of bizarre

configuration) may occur and result in a temporary dimness of vision or complete loss of vision in both eyes

Sensory disturbances are common, such as hyperesthesias, tingling and numbness in the fingers, arms, and toes, with paresthesias of the tongue, face, gums, and scalp Vasomotor disturbances are common and they may occur as pallor or flushing of the face, perspiration, urticaria, and even angioneurotic edema The duration of the attack may be from one half to twenty four hours The mechanism of the migrainous attack can be explained, according to Goltman, on the basis of an initial vasomotor spasm and secondary vascular dilatation with resulting edema of the brain and meninges

Goltman studied a migrainous patient with a postoperative opening in the skull The patient was sensitive to wheat, and following its ingestion an attack of migraine occurred which was preceded by a depression of the opening The onset of the headache was accompanied by distinct fullness of the opening probably due to a swelling of the brain, and disappearing with cessation of the attack These findings add additional evidence of the allergic nature of migraine and the pathogenesis of the attack is readily explained by a spasm of the cerebral vessels first, followed by increased vascular permeability and edema of the brain tissues

In the differential diagnosis intracranial lesions and pituitary disturbances should be ruled out by x ray studies of the head, basal metabolic rate, and glucose tolerance curves

Treatment

Since migraine may also be due to the inhalation of dust, orris root pollen, feathers wool and other inhalants, the importance of complete skin testing becomes apparent If found sensitive to inhalant factors these should be avoided if possible or hyposensitization should be carried out The elimination of the food or foods to which the patient is sensitive results in complete relief of symptoms in a large percentage of cases

Symptomatic relief of the attack may be obtained quickly with ergotamine tartrate (gynergen), subcutaneously 0 25 mg to 0 5 mg Orally, 1 mg tablets two or three times a day between attacks may diminish the frequency and intensity of the headaches

The inhalation of 100 per cent oxygen as advocated by Alvarez,

is highly beneficial in quickly relieving migrainous attacks It is best used during the prodromal period when a warning of an attack is imminent, inhaling the oxygen for one hour If the attack is not aborted, it is likely that further administration of oxygen is useless

MIGRAINE AND ALLERGIC HEADACHE FORM

1 Name ____________ Age ____ Sex ____ Occupation __________
Address ______________________________ Phone ________

2 Personal and family history of urticaria food idiosyncrasy, eczema, hay fever, asthma

3 Description of typical attack
  a time of day
  b character
  c location
  d one sided or bilateral
  e associated with nausea vomiting
  f *prodromal symptoms* (aura)
  g visional
  h flashes of light
  i dizziness
  j blurring of vision
  k canker sores
  l frequent urination
  m bad breath
  n constipation
  o indigestion
  p which eye is more affected one or both

4 Duration and severity of attack

5 Regularity of occurrences (menses menopause)

6 State of vision corrected by glasses

7 Relation to fatigue, infection emotional upsets constipation

8 Examination
  a Complete blood count Eosinophilia
  b Urinalysis
  c Kahn
  d. Basal metabolism
  e X ray of sinuses
  f Routine physical
  g Skin test to all factors

9 Food diary kept to record foods negative to skin tests

CEREBRAL EDEMA, EPILEPSY, AND CONVULSIONS OF ALLERGIC ETIOLOGY

Varied symptom complexes due to cerebral edema caused by allergic sensitivity have been recorded Choreiform movements marked personality changes and mental backwardness have been reported in allergic patients with improvement following proper allergic management

Crowe reports the following case of cerebral allergic edema which is of sufficient interest to quote in detail

A 16 year-old white male was first seen when he was 9 years old because of mental dullness sleepiness dull boring pain between the eyes and nervousness His mother and two maternal uncles had asthma Examination revealed normal height and weight for his chronological age and a retardation of his mental age with an I Q (Sanford Binet) of 71, low normal being 90 Other findings included dry coarse skin and hair infected tonsils enlarged epitrochlear glands and a palpable thyroid gland The testes although descended were smaller than normal The basal metabolic rate was minus 12 per cent The Schilling differential count disclosed an eosinophilia of 12 per cent The blood Wassermann was negative

Treatment for hypothyroidism and hypogonadism was instigated For the next six years the patient received thyroid extract and orchic substance His height increased 9 5 inches but the intelligence improved only slightly All medication was stopped on July 5 1938 In the interim he had passed the fourth grade requirements The sleepy spells had increased in frequency with as many as three to twenty a day lasting from five to sixty minutes He was advised to quit school and take up a trade

The patient was seen for the first time by Dr Crowe in March 1940 The father of the patient stated that for the past seven years the boy complained of severe one sided frontal headaches which were occasionally heralded by a swelling of the lips and beneath one eye These headaches without aura or other prodomes were always associated with drowsiness and sometimes with nausea and vomiting First the facial swelling appeared soon to be followed by headache then in about an hour came increasing drowsiness If permitted the patient would sleep but could be aroused by vigorous shaking The lethargy usually cleared in ten or twelve hours but the swelling required two or three additional hours for its disappearance The attacks had no seasonal variation began at any time

of the day, and occurred from one to three times a month Neither patient nor informant had discovered any precipitating factors

Reexamination revealed a well-developed but mentally sluggish 16 year old male with moderate edema of the lips The pulse rate was 78 per minute, the blood pressure, 115/70 mm in both arms The hair and skin were dry The thyroid was of normal size and consistency The genitals were normally developed A 4 per cent eosinophilia was found in the blood The rest of the blood count the blood chemistry, urinalysis phenolsulphonphthalein test of kidney function, and the feces were all normal The blood Kahn was negative X ray examination of the head showed no pathology Because of the familial history of allergy and the migrainous like headaches with facial edema associated with drowsiness cerebral angioneurotic edema with possible hypothalamic involvement was strongly suspected Scratch and intradermal tests were made which showed positive reactions to the following foods corn rice, wheat spinach, beans, peas, apple pear, orange, grapefruit, lemon and all seasonings

Neurologic examination revealed occasional spasmodic contractions of the head and limbs At times only one limb was involved but occasion ally all were abducted to a slight degree No objective evidences of organic disease of the central nervous system were found These findings could only be explained on the basis of a cerebral angioneurotic edema which probably involved predominantly the hypothalamus Since March 1940, when the offending foods were eliminated from the diet the patient has remained free of attacks of drowsiness and facial edema In May 1940, the patient was given purposely a piece of wheat bread Forty five minutes after ingestion periorbital edema of the right eye occurred One hour later, the patient became very lethargic Epinephrine hydrochloride 1 1000 solution, 0 2 cc, was given every ten minutes for four doses the edema and drowsiness almost cleared within the next hour There have been no recurrences since this experimentally induced one The patient has now shown greater aptitude in carrying out his present job as a mechanic than at any previous time

The cerebral edema, with foods as the excitant allergen, is best explained by local vasodilation and increased capillary permeability In this particular patient the hypothalamus was a vulnerable area Kennedy and his associates considered vasomotor changes in cerebral vessels as an important mechanism in epilepsy, arterial hypertension carotid sinus syncope, migraine, and angioneurotic edema Kennedy also observed the exposed cortex of an epileptic patient undergoing

operation with local anesthesia At the onset of the attack a primary cortical blanching followed by marked venous engorgement and brain protrusion was observed Carotid sinus syncope is explained on the basis of a momentary constriction and then marked dilatation of the pial vessels Sudden cerebral anoxemia produced in this way was held as a likely explanation of the vagal and depressor carotid sinus response

Cerebral allergy can simulate a countless number of diseases Cases have been reported where it has effected marked personality and mental changes As more of these types of patients are studied from the allergic point of view a better understanding of the altered physiology is possible and the likelihood of improvement of these heretofore hopeless conditions becomes increasingly promising

ALLERGIC ARTHRITIS

Joint Involvement Due to Allergy

The possibility that bacteria and food may be causative factors in some forms of arthritis has been the subject of investigation by many workers due to the fact that serum sickness and drug allergy are frequently accompanied by joint symptoms

The association of arthritis and asthma in the same patient occurs with sufficient frequency to warrant the conclusion that at least certain types of arthritis may be anaphylactic in origin These patients usually develop asthma in later life between 40 and 50 years of age and some bacterial infection in the nasal sinuses or bronchi is responsible for this type of asthma The associated arthritis may likewise be a manifestation of an allergic reaction occurring in the synovial membranes due to a bacterial hypersensitivity

Freiberg and Darst reported on an extensive series of clinical cases of arthritis which they studied making cultures from all possible areas of focal infection and from the stools Individual vaccines were made with each organism isolated Skin tests were made with these vaccines and those giving positive reactions were combined *into one vaccine and minute hyposensitizing doses administered* In a series of 13 patients who had arthritis for from eighteen months to fourteen years they reported 7 cured 3 with marked improvement 1 with improvement and only 2 with no improvement

The association of arthritis with mucous colitis occurs with sufficient frequency to investigate the role of foods as a causative agent in some types of arthritis Positive skin tests to various food proteins have been found in arthritis patients and in some who had an associated mucous colitis On removal of the offending foods, the arthritis and colitis improve The addition of the foods to the diet results in a return of symptoms

Vaughan reported on the treatment of 100 arthritis patients with minute hyposensitizing doses of autogenous or stock vaccines with the following interesting results 10 per cent were completely relieved of their symptoms 37 per cent were improved, and only 27 per cent were not affected

Hydrarthrosis

Bilateral chronic synovitis or intermittent hydrarthrosis appears in attacks of such striking periodicity that an allergic basis for these attacks is strongly suggested In 1924 Miller and Lewin were the first to suggest that idiopathic hydrarthrosis is a sensitization disease, basing their evidence on the satisfactory response of this condition to intravenous injections of peptone

Judging from the sparse literature since this observation, very little attention has been given to this group of cases, with the exception of Rowe, who reported a patient with this disease due to food sensitivity Skin tests were negative and the causative foods were determined by elimination diets

Philip Lewin and the author, in 1936 reported the occurrence of an intermittent hydrarthrosis of both knees in a boy of 16 Stiffness and swelling of the knees had occurred every two or three months intermittently for ten years The swellings came on suddenly and disappeared usually within twenty four hours No other allergic symptoms were present, but the boy s father had hay fever and a paternal uncle had hay fever and asthma His mother had had urticaria from eating tomatoes or strawberries Intradermal tests to foods and inhalants showed a positive reaction to English walnuts only Passive transfer tests were likewise positive and after eating walnuts a typical attack followed within seventy two hours This patient abstained from eating all nuts and no further attacks occurred up to the present time

Many additional reports of food hypersensitivity as a causative factor in this disease have been reported in the literature since

The possibility of food allergy should be considered in every case of idiopathic synovitis A personal or family history of the common allergic diseases namely asthma hay fever urticaria angioneurotic edema eczema or migraine increases the likelihood that some form of sensitization is present Food sensitization should be ruled out by skin tests with all the foods entering into the routine diet of the patient If these food tests are negative elimination diets should be tried

Treatment

When foods are found to be a factor in arthritis or intermittent hydrarthrosis their elimination from the diet results in marked improvement of symptoms

In some types of arthritis the elimination of foci of infection plus hyposensitization using minute doses of an autogenous or stock mixed vaccine often results in considerable relief of symptoms

It seems suggestive that some cases of arthritis which are of long standing and resistant to therapy may be of an allergic nature and it is possible that allergic studies may hold out some hope for these sufferers

GENITOURINARY TRACT ALLERGIES

Involvement of the urinary bladder with symptoms of cystitis tenesmus and dysuria has been described as due to hypersensitization to foods and locally from medication or contraceptives No local findings may be apparent Enuresis in children has been reported to be caused by allergy to foods and relieved by their avoidance in some cases Frequent and painful urination tenesmus urinary retention (urethral edema) renal colic vulvar irritation and balanitis may occur as the result of inhalant ingested or contact allergens During the pollen season symptoms in the urinary tract are frequently observed and dysmenorrhea may occur Ingestion of wheat eggs milk or fresh fruits may likewise cause symptoms in patients allergic to these foods

Local sensitivity may result from drugs used locally douches washes lotions ointments and contraceptives These substances act

as contactants Improvement follows the avoidance of the allergic factors although it is important for the urologist to rule out any organic disease or infection Where other allergic disorders are present in the patient symptoms occurring in the urinary tract should be suspected as being probably allergic The possibility of a sensitivity even in renal colic should not be overlooked

The kidney can be involved by allergic reaction as seen in serum sickness drug allergy—especially sulfonamides purpura and peri arteritis nodosa Likewise acute glomerulonephritis complicating scarlet fever may be an example of bacterial allergy

CARDIOVASCULAR ALLERGY

That the cardiovascular tissues may be the seat of allergic reactions is not surprising since every organ of the body contains capillaries and smooth muscle tissue necessary for the allergic mechanism Many reports have appeared in the literature during the past decade on allergic reactions occurring in cardiovascular tissues yet cardi ologists and even allergists have been reticent in accepting these observations

Experimental evidence on animals has shown that there are dis turbances of conduction in the heart of the guinea pig and heart block has been demonstrated in the rabbit during anaphylaxis Criep made a thorough electrocardiographic study of the effect of ana phylaxis on the guinea pig and rabbit heart and found changes in the T wave similar to that found in coronary occlusion Brady cardia partial or complete heart block inversion of the T wave with a shortened R T interval and a high T take off and auricular and ventricular fibrillation suggested a myocardial anoxemia which Criep concluded was anaphylactic in nature

Isolated hearts of guinea pigs sensitized to horse serum react upon exposure to small amounts of antigen by a temporary increased rate alterations in the amplitude of contractions electrocardiographic abnormalities and a reduction in the rate of flow through the coronary arteries Wadsworth and Brown reported a case of acute carditis following serum sickness and Harkavy found eosinophilic infiltrations in the walls of the pulmonary arteries of a patient who died of asthma

Uncomplicated bronchial asthma even of long duration produces

no typical demonstrable changes in the heart and blood vessels Asthma therefore does not cause any strain on the normal heart Cardiac findings in an asthmatic patient are due to other causes than the asthma and it is possible for a localized allergic reaction to occur in the heart tissues similar to that described in periarteritis nodosa

Duke has produced attacks of angina, tachycardia and ventricular extrasystoles in patients with physical allergy by the use of heat, cold, and effort—and could terminate these attacks by the opposite medium or by the use of epinephrine

Paroxysmal tachycardia, extrasystoles, and angina have been reported in patients hypersensitive to foods, and when the offending foods were eliminated from the diet these attacks disappeared Coffee has been reported responsible for angina and, upon its elimination, no further attacks appeared Eggs have been reported as a cause of gastrointestinal allergy occurring with numerous extrasystoles Atypical anginal pain frequently occurs during the hay fever season and is relieved by injections of pollen extract

Coca calls attention to an increase in heart rate occurring in patients following the eating of foods to which they are sensitive and suggests the use of this increase in rate as a clinical test for food sensitivity

Davison, Thoroughman, and Bowcock, review the literature on cardiovascular allergy and report the occurrence of extrasystoles, paroxysmal tachycardia auricular fibrillation and flutter, and hypertension caused by food allergies in 15 of their patients Control of the allergic factors in this group resulted in improvement in a majority of the patients Tobacco sensitivity has been shown to be an etiologic factor in Buerger s disease, angina pectoris angiospastic crisis gastric ulcer and cardiac arrythmias

Harkavey has found as high as 87 per cent of patients with thromboangiitis obliterans allergic to tobacco extract Likewise, in a series of 71 male patients with coronary artery disease who were smokers, 43 per cent reacted positively to tests with tobacco extract

HYPERTENSION

At the height of an asthmatic attack there is usually a fall in blood pressure, while between paroxysms the blood pressure is usually normal or below normal It has been observed that when hyper

tension accompanies asthma, a fall in blood pressure occurs following *the injection of epinephrine* and the relief of the asthma attack. These observations might indicate that the hypertension may be caused by an allergic reaction or that it is sometimes an accompaniment of the asthmatic attack.

Several reports of hypertension due to food allergies have appeared in the literature. Injections of epinephrine were followed by a drop in the blood pressure, and, following the elimination of foods to which these patients were found allergic, a return to normal pressure occurred.

The *vasospastic response* in the blood vessels of the vital organs particularly the renal organs, accompanying an allergic reaction in these tissues may be followed by release of *angiotonin* or *rennin* with the appearance of hypertension. This mechanism is offered as an explanation of essential hypertension on an allergic basis.

Obviously additional study is needed to determine the role of allergy in cardiovascular disturbances. The possibility has been pointed out and the probability of an allergic etiology should be thought of in some of these disturbances.

PHYSICAL ALLERGY

It is a common observation that change in weather, especially from warm to cold may bring about an asthmatic attack in an asthma patient by reason of a contributory factor. This, however, has no bearing on physical allergy although at times it may actually be a factor.

By physical allergy we mean the occurrence in allergic patients of asthma, urticaria, angioneurotic edema, and vasomotor rhinitis following mechanical *irritation*, and exposure to heat, cold, light and effort. We are chiefly indebted to Duke for recognition of these phenomena and he proposed the term physical allergy in his report in 1924. Duke suggested that a histamine like substance might be released into the local tissues and later this explanation of the mechanism involved was again advanced by Lewis.

Reactions from physical allergy may be local and general or systemic. Local reactions occur at the site of contact with the excitant, such as heat, cold, or the actinic rays, while systemic reactions may

occur in any tissue of the body Conjunctivitis sneezing nasal ob struction asthma erythema of the skin pruritus urticaria angio-neurotic edema disturbances in the gastrointestinal tract such as abdominal pain and diarrhea following the ingestion of cold drinks or food or hot food or drinks may be due to unusual sensitivity to heat or cold These patients may have an eosinophilia and usually respond to an injection of epinephrine Constitutional reactions to cold may be so severe as to result in syncope and this may be a cause of drowning in good swimmers who suddenly plunge into cold water Swimming may likewise result in effort or heat in heat sensitive individuals and drowning may occur in these people for the same reason

The exciting agents responsible for physical allergy are cold heat light mental and physical efforts and mechanical irritation The reactions produced are of two types (1) Contact reactions produced at the site directly exposed to the physical agent and (2) reflex like reactions in which the symptoms produced are widespread and in volve distant parts of the body

When ice is applied locally to the face of a patient sensitive to cold and urticaria results a contact type of allergy is present Should an asthma attack result instead a reflex like type of allergy has occurred

Duke has described the following type of contact reactions Orbital reaction caused by exposure of the face to cold air and by light nasal reactions due to the breathing of cold air skin reactions (urticaria pruritus erythema) due to cold light burns and mechanical irrita tion eczema of the hands face and ears due to cold and light shock caused by cold and light eosinophilia caused by cold mechanical irritation and light severe abdominal pain due to the ingestion of ice cream cold drinks or iced foods

As a rule patients who are sensitive to one agent such as cold are rarely sensitive to another agent such as light or heat

Tests for Cold and Heat

Duke tested patients for cold allergy by vigorously rubbing large pieces of ice over the chest back and arms for three or four minutes and waiting for ten minutes for a reaction to occur such as urticaria asthma or rhinitis The allergic response to heat or cold is not necessarily to fixed degrees of temperature but may be to changes

in temperature Therefore, alternating the test to heat and then cold may produce the allergic response by the mere fact that the temperature is changed suddenly

To test sensitivity to heat the patient is exposed under a 1500 watt nitrogen lamp with an appropriate reflector held at a distance of 18 to 24 inches from the skin Heat is applied to the chest or back for a ten minute period or until symptoms of a reaction occur When reactions occur to heat, the application of cold quickly counteracts the reaction, and vice versa The injection of epinephrine also controls the attack Horton, Brown and Roth in 1936 described a simpler, more practicable pair of tests for cold and heat sensitivity The former consists of immersing the hand and part of the forearm in water at about 9° C or 48° F, for six minutes The skin becomes blanched and, following removal from the water, the local pallor changes to redness slight edema, and an increase in local temperature The systemic reaction of asthma, urticaria or rhinitis usually appears in from three to six minutes after removal of the hand from the water Any of the shock tissues of the body may be affected and a fall in blood pressure, rise in pulse rate, dizziness, or syncope may follow These reactions may be controlled by placing the hand in warm water If a tourniquet is applied above the elbow during the test these observers noted more severe and prolonged reactions, lasting often three times longer Reactions occur usually within six minutes after release of the tourniquet To control reactions the reapplication of the tourniquet may be required, thereby blocking the absorption of H substance into the circulation

The heat test is conducted similarly, dipping the hand in warm water of 104° to 108° F or as warm as can be comfortably tolerated first without and later with a tourniquet

Ultraviolet Test

Exposure of one arm or the upper part of the body may be done with a quartz mercury vapor lamp for from one to two minutes at a distance of 36 inches from the skin Direct exposure of an arm to the sun s ray may also be done The reaction ensuing is usually an urticaria or a dermatitis and prolonged exposure may result in asthma angioneurotic edema migraine, or allergic coryza

Effort Test

Heat sensitive individuals are usually affected by heat manufactured within the body by effort such as exercise, which would not materially affect a normal individual For example, climbing a few stairs, touching the floor a few times with both hands, or raising dumbbells over the head several times, might result in tachycardia, dyspnea, vertigo, and syncope in a heat allergic individual, whereas the same degree of exertion in a normal person would have no effect Should asthma, urticaria, migraine, or rhinitis follow, an allergy to effort or heat is apparent The application of cold controls the allergic symptoms produced by effort

Mechanical Irritation

By irritating the skin mechanically with a stiff brush or stroking the skin several times with a tooth pick, an urticarial response follows similar to dermographia The irritation may be applied to an area of the body like an arm and the entire body may become affected with a generalized urticaria

Contact Reactions Caused by Light

An ordinary exposure to light in a hypersensitive patient may result in a severe urticaria or inflammation of the skin involving the exposed parts

The forehead, cheeks neck, and backs of the hands are usually involved These reactions occur in the summer and usually disappear in the fall

Duke described an urticarial dermatitis, affecting particularly women following the exposure of the skin to the rays of the sun He called this condition urticaria solaris A severe urticaria with marked itching and inflammation of the exposed parts of the body results within a few minutes from exposure to direct sunlight or ultraviolet light In some instances this inflammatory like reaction would appear several hours after exposure Mild repeated exposures of the skin to direct sunlight or ultraviolet light results in some increased tolerance of the skin However, in a short time this tolerance is lost Specific wave lengths may be responsible for these reactions, some may

react to the ultraviolet spectrum while others may be sensitive to the infrared or blue portion of the spectrum

Contact Reactions Caused by Cold

The symptoms resulting from exposure to cold in sensitive individuals vary with the tissues involved and the degree of exposure When the reaction occurs in the skin, urticaria and edema with severe itching result In many instances the temperature of the water is between 10° and 15° C, and a temperature of 20° C or a freezing temperature would have no effect Systemic reactions such as syncope, fall in blood pressure, or even unconsciousness may result if large areas of the body are exposed as in swimming

Asthma may result following the exposure of sensitive patients to breathing cold air Sneezing, watery nasal secretion, and nasal blockage may result from the breathing of cold air by patients with sensitive nasal mucosae

Contact Reactions Caused by Heat

An urticarial skin reaction may occur from exposure to various degrees of heat Duke has described reflex like reactions from heat which occur more often than local reactions

Cutaneous Reactions Due to Mechanical Irritation

Slight stroking of the skin in certain sensitive individuals results in erythema and wheal formation This condition is known as dermographia or factitious urticaria They are similar to cold or light sensitivity except that they are caused by mechanical irritation

Reflex like Reactions

Reactions resulting from contact allergy of a physical nature may occur in the nose, skin, or bronchi separately or all three systems may participate in the production of symptoms Many of these patients may also show allergic reactions to foods Thermal or heat sensitiveness is usually caused, either by a local or general increase in heat or calories whereas cold sensitiveness results from a local or general decrease in temperature The results of physical or mental effort may cause symptoms of heat hypersensitivity by the generation of heat within the body In fact, Duke was of the opinion that heat hypersen

sitivity is much more common than cold and those patients who react to heat do so only after a previous exposure to cold

Likewise cold sensitive patients react to cold only after exposure to heat In the majority of patients it seems that reactions occur more often by a change in temperature and the contrast between temperatures may be responsible for symptoms in this type of allergy

Laboratory Findings Some patients may have an increase in eosinophils in their blood However this is not constant

Cryoglobulin (cold precipitable serum globulin) is not present in urticaria due to cold Cold hemolysins are likewise not present in patients with urticaria due to cold

In a number of instances the sera of patients with urticaria due to cold have been reported to sensitize passively normal skin to cold but a large number of negative reports have cast doubt on the occurrence of passive transfer of this type of reaction

Recently Sherman and Seebohm reported a patient with urticaria due to cold who showed positive passive transfer reactions to the normal skin Attempts to demonstrate reversed passive transfer and to isolate an antigen from normal skin by cold which would react with the serum were unsuccessful

Treatment

The opposite type of physical agent is applied to counteract the effect of the reaction in physical allergy If a reaction is obtained with cold heat is applied until the symptoms disappear Likewise in heat sensitive reactions cold is applied Light sensitive patients must use protection to the hands by wearing gloves and a veil to protect the face and neck Various creams particularly the antihistaminic creams and ointments applied to the exposed surfaces of the body are helpful in preventing allergic reactions in light sensitive patients

In cold sensitive patients relief is obtained by immersing the hand in water at 10° C for one to two minutes twice daily for three to four weeks In heat sensitive patients the hand is immersed in cold water first increasing gradually to warm Light sensitive patients are exposed gradually to increasing doses of ultraviolet light or direct sunlight

During an acute attack of allergy due to one of the physical agents

subcutaneous injection of epinephrine 0 5 to 1 cc of the 1 1000 aqueous solution or in oil gives immediate relief The antihistaminic drugs given in doses of 50 mg three or four times a day provide symptomatic relief

The subcutaneous use of solutions of these drugs is likewise beneficial together with oral doses The effect of these drugs is usually symptomatic and only temporary The daily subcutaneous injection of increasing doses of histamine is effective in some patients

Theories of the Mechanism of the Physical Allergies

Duke was of the opinion that the reflex like reactions caused by *heat or cold are due to a disturbance of the heat* regulating mechanism Many observers believe that histamine or H substance is liberated into the circulation from the action of the physical agent upon the skin of the sensitive patient

There is as yet no proof that the physical allergies are due to any antibody antigen mechanism

BACTERIAL ALLERGY

Sensitization to bacterial extracts was first demonstrated in 1907 by Rosenau and Anderson who produced anaphylactic reactions to typhoid colon anthrax and tubercle bacilli

Avery in 1923 demonstrated a specific pneumococcus polysaccharide which gives positive intradermal skin tests in patients recovering from pneumonia These antigens probably belong to the hapten group by combining with serum globulin to form a new protein complex with a biological specificity of its own

The tuberculin reaction is a delayed positive reaction occurring *twenty four to forty* eight hours following the intradermal test Infection with the tubercle bacillus is necessary before the test becomes positive and passive transfer tests are negative with tuberculin There is evidence that the reaction *depends upon sensitization to decomposition* products arising from an inflammatory tissue reaction producing a nucleoprotein in the body

The hapten type of allergy has *also been produced by Brucella* abortus melitensis and suis Bacillus mallei gonococcus Treponema pallida Streptococcus hemolyticus and Streptococcus viridans

Likewise rheumatic fever and atrophic arthritis may *represent*

bacterial types of allergy In rheumatic fever the occurrence of upper respiratory infections and the development of rheumatic fever strongly suggest a sensitivity to streptococci These organisms are absent in the blood and tissues in rheumatic fever and this is additional evidence in favor of the allergic nature of this disease

Subacute bacterial endocarditis may likewise be a manifestation of an allergic reaction occurring on a previously sensitized site the previously damaged heart valves in rheumatic fever with a filtering out of enormous amounts of Streptococcus viridans organisms on the valve leaflets with the production of inflammatory cauliflower like growths

Hemolytic streptococcus filtrates have been used in rheumatic fever patients and a definite reduction in attacks has been reported A high degree of immunity can be produced and this method offers the best possibilities in preventing recurrences Injection with streptococcus filtrates results in immediate large skin reactions and it is important to treat these patients with small amounts over a long period of time in order to produce an immunity Likewise in atrophic or infectious arthritis small doses of vaccine following the principle used in coseasonal pollen treatment is highly beneficial which would indicate an allergic basis for these diseases

In asthma and allergic rhinitis the role of bacteria is very much disputed They probably rarely cause allergic rhinitis and asthma but may be contributing factors as evidenced by the frequent occurrence of asthma following an upper respiratory infection Colds only cause asthma in an allergic individual Scratch or cutaneous tests with bacterial proteins are usually negative while intradermal tests give delayed positive reactions equally in nonallergic and allergic individuals In general removal of foci of infection is indicated but relief of asthma or rhinitis does not occur Treatment of rhinitis and asthma with bacterial vaccines may result in temporary relief in some patients but the author feels that this is due to a nonspecific effect similar to the relief obtained at times with the use of any foreign protein such as peptone lactigen etc

Periarteritis Nodosa

The first observation that periarteritis nodosa may be an allergic disease was made by Gruber in 1925 Kline and Young in 1935

reported three patients in whom allergy was demonstrated Cohen Kline and Young in 1936 stated that this disease is due to a severe allergic reaction occurring in the blood vessels and a diagnosis could be made clinically on a biopsy The occurrence of asthma and periarteritis in the same patient has been reported by various observers such as Rackemann and Greene in eight patients and Berger and Weitz in one patient The author has observed two patients at the Cook County Hospital both young males 25 and 28 years of age with hay fever asthma and food sensitivities who developed typical findings of this disease proved by biopsy of muscle tissue

Rich in 1942 reported the occurrence of this disease in seven patients who had serum sickness as a result of administration of serum Four of these patients in addition had been given sulfonamide drugs Rich likewise later reported the occurrence of generalized lesions of periarteritis nodosa in another patient who had fever and conjunctivitis following continued sulfathiazole administration

His conclusions are that the continued use of a sulfanilamide drug or a foreign serum after symptoms of hypersensitivity have occurred or the injection of a single large amount of foreign serum carries the danger of producing vascular damage of the periarteritis type

Rich and Gregory in 1942 also demonstrated the production of periarteritis nodosa in rabbits following serum sickness Acute diffuse glomerulonephritis occurred in a number of the rabbits suffering from serum sickness and this would indicate that some cases of glomerulonephritis occurring in man may be due to hypersensitivity

Periarteritis nodosa is a necrotizing arteritis affecting the medium sized and small arteries of the body accompanied by systemic symptoms of infection with additional local symptoms depending on the organs involved The visceral arteries are more frequently involved than the peripheral arteries so that internal hemorrhages renal involvement resembling acute glomerulonephritis and gastrointestinal hepatic cardiac or organic nervous disease symptoms may appear Cutaneous hemorrhages urticaria purpura and tender reddened subcutaneous nodules appear in the extremities A high blood eosinophilia is usually present at times reaching 60 and 70 per cent as in the author s two patients When the superficial arteries are involved the characteristic nodules may be felt along the course of

the artery, or a biopsy of a tender muscle may disclose a necrotizing arteritis, typical of this disease

It is very likely that this disease is a manifestation of a hypersensitivity similar to drug allergy, serum sickness, or bacterial allergy with the allergic response occurring in the blood vessel walls as a result of the union of antigen and reagin in these tissues

Chapter XII

Serum Sickness and Prophylaxis

In a large percentage of individuals who are injected with a foreign serum, reactions occur which at times may be serious or even fatal It is estimated that 90 per cent of people are affected following injections with a foreign serum The physician should be acquainted with the manifestations of serum disease because the symptoms are so variable that unless the disorder is recognized or anticipated, a diagnosis of some other acute disease will be suspected

There are three distinct types of serum sickness

1 Ordinary serum sickness
2 Accelerated serum sickness
3 Atopic or allergic serum sickness

ORDINARY SERUM SICKNESS

This is the most common type, and it occurs after the administration of *horse serum, with a lapse of six to fourteen days,* usually nine to ten days following the injection The symptoms may be *urticaria,* angioneurotic edema, joint pains, fever, skin eruptions, and even asthma An eosinophilia may or may not be present The severity of the symptoms is dependent upon the amount of serum injected and the manner of administration, whether subcutaneously, intramuscularly, or intravenously If a large amount of serum is injected intravenously, 100 per cent will develop serum sickness If the same amount is injected intramuscularly, about 60 to 70 per cent will develop serum sickness, whereas a subcutaneous injection will affect about 40 per cent

Heredity is not a factor in its production, nor is the mechanism involved clearly understood These people are not especially sensitive to horse serum and scratch, intradermal, and ophthalmic tests to horse serum are negative Various antibodies, including heterophilic antibodies, are demonstrated in the patient s serum during serum sickness however, these have not been shown to be involved in its production There is, as yet, no proof that it is an antibody antigen reaction or that circulating antibodies or reagins play any etiologic role

The skin eruption of serum sickness appears at the site of injection It may be urticarial, rubellaforme, scarlatiniforme, erythema multiforme, erythematous, or petechial The eruption usually lasts two to three days and may persist for five to seven days Fever of 100 to 104° F may follow a chill and persist for ten to fourteen days Enlargement of the superficial lymph glands usually appears with the onset of fever and the skin eruption At the same time the spleen may become enlarged and palpable Swelling redness, and tenderness of the joints, involving the small joints of the hands and feet, temporomaxillary joints, and those of the elbows ankles and knees frequently occurs and fluid containing horse serum has been isolated from aspiration of a joint on several occasions Pleural and pericardial effusions have been encountered in patients with serum sickness

Laboratory Findings

The blood reveals a constant leukopenia with a relative lymphocytosis and an eosinophilia may or may not be present A drop in blood pressure and diminished coagulability of the blood have been observed The sedimentation rate of the erythrocytes is usually normal, but may be elevated in the presence of a complicating infection There are no abnormal blood chemistry, urine or spinal fluid findings

ACCELERATED SERUM SICKNESS

This reaction follows in a patient who has received an injection of a foreign serum for the second time and at an interval of longer than four weeks The reaction may be the same as that of ordinary serum sickness, or it may be very severe or even fatal

Should large amounts of serum be given intravenously, the symptoms may be very severe and even immediately fatal

Various antibodies can be demonstrated in the blood, such as precipitins, anaphylactic antibodies, and reagins Positive skin tests and passive transfer tests are present in this type

It is rational to assume that the accelerated variety of serum sickness is an acquired form of allergy to serum as a result of a previous injection These reactions are more prone to appear following the use of horse serum for hemorrhage, scarlet fever antitoxin, tetanus antitoxin, and streptococcus antitoxin serums

ATOPIC OR ALLERGIC SERUM SICKNESS

This type is the most important for the physician to guard against since it causes immediate death It is most unfortunate and dramatic for a well patient to walk into a physician's office, be given as little as 0 1 cc or 0 2 cc of horse serum, and, almost before the needle can be removed, groan, turn ashy white, collapse, and become lifeless before epinephrine can even be administered

Three distinct types of pathology have been described on post mortem examination The first type is the hepatosplanchnic enlargement in which the liver and splanchnic vessels are so engorged that other parts of the body have no blood This is also seen in anaphylactic shock in dogs

The second is the pulmonary emphysema variety, and spasms with distention of the bronchioles are found The patient does not wheeze but just stops breathing Anaphylactic death in guinea pigs reveals these same findings

The third type reveals extreme right heart failure, with tremendous dilatation, and is similar to anaphylactic death in rabbits

The diagnosis is made on the history of a previous injection of a foreign serum and a family history of some allergic disturbance such as hay fever, asthma eczema, or urticaria Before administering any serum the ophthalmic test should be done It consists of instilling one drop of a 1-100 dilution of horse serum into the conjunctival sac. Itching of the eye and reddening of the conjunctiva indicates a positive reaction This test has a limited value, however, in children since it may be negative in the presence of horse serum sensitivity If the 1 100 horse serum is negative, the test may be repeated, using 1 drop of a 1 10 dilution If the opthalmic test is negative, a scratch

test should be done, applying 1 drop of a 1 100 horse serum dilution If the test is negative after an interval of fifteen minutes, an intradermal test is done with 05 cc of a 1 100 horse serum dilution, then 05 cc of a 1 10 dilution, and finally, 05 cc of concentrated serum When these tests are negative, it is safe to give the serum Serum sickness may still develop, however, but no severe immediate allergic reaction will develop

Should the individual give a history of allergy, regardless of the type of allergy, and serum injection is contemplated, the above tests must be given If the patient reacts, even slightly, serum should be withheld and some other variety of serum used, as goat serum or toxoid

A despeciated horse serum globulin is now obtainable in which the albumin fraction has been removed and the globulin which contains the antibodies is retained This type of serum may produce anaphylaxis and even death, but serum sickness reactions are not as frequent

Despeciated horse serum is absolutely contraindicated to any patient who reacts specifically to the conjunctival or intradermal and scratch tests

Prophylactic toxoid can be given in two injections a week apart A third injection of toxoid causes a rapid rise in the antibody titer and serum reactions do not occur Toxoid can be used prophylactically in tetanus and diptheria immunization giving the two injections prophylactically and the third injection may be given at a later period at the time of exposure

Allergy	*Eye*	*Intradermal*	*Scratch*	*Injection of Serum*
Serum shock	plus	plus	minus	None
History of allergy	plus	plus	minus	None
Nonallergic	plus	plus	minus	None
Nonallergic	plus	minus	minus	Carefully
Nonallergic	minus	minus	minus	Yes

Schedule of dilutions

Concentrated Serum 0 5 cc	*plus*	Normal Saline 4 5 cc *equals* 1 10 dilution	Normal Saline 4 5 cc *plus* 0 5 cc. of 1 10 dilution *equals* 1 100 dilution

In doing the tests, always begin with the 1 100 dilution, then use the 1 10 dilution, and finally, the concentrated serum Wait fifteen minutes between tests for reactions to appear

THE ARTHUS PHENOMENON

This reaction was first described by Arthus, in 1903 in experiments on the rabbit, and the same type of reaction occurs in the human following repeated intradermal, subcutaneous, or intramuscular injections of a foreign serum The local reaction is an inflammatory swelling which rapidly undergoes necrosis and gangrene, resulting in extensive sloughing of the involved area The Arthus phenomenon invariably results from repeated serum injections and when local serum reactions from a previous injection are still present The injections need not necessarily be given in the same area each time in order to cause this severe reaction

Clinically, positive tests to horse serum, goat serum, or rabbit serum are found, as well as positive passive transfer studies

Precipitin in large amounts is present in the blood serum of these patients Most observers believe that the Arthus phenomenon results when antigen and antibody meet within the tissues The antibody is probably precipitin Many deaths have been recorded in the literature from extensive sloughing of large areas of gangrenous tissue resulting from repeated injections of serum in hypersensitive patients To avoid these reactions, patients should be tested first to horse, goat, or rabbit serum and repeated serum injections should never be given when a local or systemic reaction is still present following the previous serum injection

The incidence of allergic reactions from convalescent human serum is reported to be around one per cent Pooled convalescent serum from several donors will dilute allergic antibodies and fewer allergic reactions will occur

ALLERGY FROM BLOOD TRANSFUSION

Transfusion of blood from an allergic individual has resulted in passively sensitizing a normal recipient Loveless, in 1941, demonstrated that blood donors who were hypersensitive to ragweed pollen transferred this hypersensitivity to recipients previously not allergic to pollen The sensitizing factor present in the transfused blood was removed and taken up by the nasal mucosa, conjunctiva, and skin

Cutaneous sensitivity could be detected as early as one and one-quarter hours following transfusion Nasal and conjunctival tests were positive from two and three quarters to twenty four hours following transfusion Antibodies acquired through transfusion are removed from the circulation in less than twenty four hours and appear in the skin first and later in the conjunctiva and nasal mucosa The duration of the sensitivity may persist from twenty four days to twenty two weeks From the clinical and practical point of view, allergic individuals should not be used as blood donors

The following outline describes the cutaneous tests employed to determine the presence or absence of sensitivity to the serum—usually horse serum—in the case of tetanus

Technic

A *Scratch test*

1 Make 2 superficial scratches on front (volar) surface of either forearm

2 Apply a drop of 1 10 dilution (0 1 cc serum in 9 9 cc of isotonic NaCl solution) over upper scratch (use lower scratch as control)

3 If, after 15 to 20 minutes, no local or constitutional reaction occurs proceed to the cutaneous test, described under (4)

B *Intracutaneous test*

4 Raise a tiny wheal (smallest amount of serum practicable) on the front (volar) aspect of either forearm

5 Use the following dilutions
Presumptive positive sensitivity 1 10 000 dilution
Negative sensitivity 1 1000 dilution
Under all circumstances at 15 to 20 minute intervals, if

Remarks

1 Positive local reaction area of edema about 0 5 inch in diameter with erythema (like a wheal), with or without finger like projections at circumference (pseudopodia), appears within 15 to 20 minutes

2 A negative reaction does not always mean that it is safe to give serum

3 A positive reaction does not always indicate that it is dangerous to give serum

4 But when a positive reaction does prove to indicate clinical sensitivity the sooner the reaction and the greater its size, the greater is the likelihood of a constitutional (anaphylactic) reaction

5 The tests must be given each time serum is to be injected (may change from positive to negative or vice versa)

6 Constitutional reactions various forms of 'serum sickness' to skin tests are identical with those

Technic	*Remarks*
preceding dilutions give negative readings, repeat tests in the order of the next lower dilution 1 1000, 1 1000, 1 10	which follow injections of serum for prophylaxis or therapy, they may follow with either negative or positive reactions

Presumptive diagnosis of serum sensitivity (a) presence of allergic complaints (hay fever, asthma, hives, food sensitivities, migraine, eczema, etc) in the patient or relatives (past or present), (b) serum injections in the past (tetanus, diphtheria, pneumonia, etc.), without any reactions (early or late)

Probable sensitivity (a) skin reactions (or ophthalmic reaction) positive on previous occasions, (b) allergic complaints (sneezing, coughing, wheezing, burning eyes, stomach ache, hives itching headache, etc) when around horses (if horse serum is to be used) or cows (if bovine serum is to be used)

Positive sensitivity (a) allergic difficulties from previous injections of horse serum, (b) constitutional (anaphylactic) reaction from cutaneous or ophthalmic tests for sensitivity, (c) constitutional reaction during present injections

The following outline should be helpful in avoiding mild to fatal reactions to prophylactic or therapeutic doses of antitetanus serum

A Administer tetanus antitoxin only if essential

1 Are the indications present? Can care of the local lesion by itself be adequate?

2 Can tetanus toxoid be used in place of tetanus antitoxin? A booster dose of 0 1 cc of either fluid or alum precipitated toxoid is adequate even though tetanus toxoid was injected *five to six* years previously In certain instances (delay, strong local lesions, hemorrhage) a booster dose of tetanus toxoid should be supplemented with 10 000 units of tetanus antitoxin

B Determine whether the patient is sensitive to horse serum (history, physical examination skin tests)

C Under all circumstances adopt the following measures to avoid reactions to tetanus antitoxin

1 Administer an appropriate antihistamine compound, in sufficient quantity, orally or parenterally (when feasible), at least 30 minutes before injecting tetanus antitoxin (no matter what the history, physical examination, or tests reveal)

2. A syringe containing 2 cc. of epinephrine hydrochloride (1:1000) should be immediately available to treat any acute serum reactions.
3. A syringe containing 5 cc. of diphenhydramine hydrochloride (for intravenous injection) should be immediately available to assist in the control of acute serum reactions (1 to 2 cc. to be injected, and repeated as necessary).
4. In the presence of a probable or positive diagnosis of serum sensitivity, the patient should be hospitalized for at least twenty-four to forty-eight hours.
5. All patients who receive tetanus antitoxin (independent of history, physical examination, or tests) should be given one of the antihistamine compounds for fourteen days to avoid all forms of serum sickness.
6. In the presence of a presumptive, probable, or positive diagnosis of serum sensitivity, in addition to antihistamine therapy, hospitalization, and epinephrine hydrochloride (as needed), employ the following method of hyposensitization:

Dilution of antitoxin	*Volume*	*Route*	*Interval and remarks*
1:1000	0.1	Subcutaneous	15 minutes between each injection of antitoxin
	0.2		
	0.3		
	0.5		
	1.0		
1:100	0.1	Subcutaneous	In case of reactions during course of injections treat reactions; continue dose preceding reaction, gradually increase dose if further difficulty is not encountered
	0.2		
	0.5		
	1.0		
1:10	0.1	Subcutaneous	In case of reactions increase intervals between injections to 30 minutes
	0.2		
	0.5		
	1.0		
None (undiluted)	0.1	Subcutaneous	
	0.2		
	0.5		
	1.0		
	Rest of serum as one dose intramuscularly		

D. At an appropriate interval after serum prophylaxis (four to six weeks after the newly recommended dose of 5000 to 10,000 units) inject 0.5 cc. of alum-precipitated tetanus toxoid (use the newly marked purified products) and repeat dose in one month. Thus, on subsequent occasions, tetanus toxoid may be employed in the form of booster doses in place of antitetanus serum.

Chapter XIII

Preparation of Extracts

Extracts used for cutaneous tests intradermal tests and treatment may be purchased from various sources if the physician has not sufficient time or laboratory space for their preparation In performing cutaneous tests the commercial dry powders are recommended since their preparation is somewhat time-consuming

The solutions used in intradermal testing and treatment are prepared in various ways by different allergists the main differences being in the formula of the extracting fluid used The author prefers to use an isotonic 5 per cent dextrose solution with 0 4 per cent phenol as a preservative It is the least irritating and does not deteriorate as rapidly as saline solutions

Dextrose	1½ ounces
Sodium bicarbonate	30 gr
Phenol	75 gr
Distilled water to make	1 qt

Pollen Extracts

Commercial dry pollen is purchased since its collection and drying are time consuming

Three grams of the dry pollen are placed in a filter paper in a glass funnel and anhydrous ether is slowly poured over it until the residue runs clear The yellow liquid contains the fat portion which can be evaporated and used in patch tests in patients with weed dermatitis due to the fat element

The pollen is allowed to dry for about one to two hours and it is then added to 100 cc of the diluent in a stoppered flask and placed in the refrigerator It should be slowly shaken at intervals and allowed to extract for forty eight hours After forty eight hours the solution is filtered through a Seitz filter tested for sterility and is now ready for use This concentration is a 3 per cent solution and is diluted as follows

1 cc of the 3 per cent solution plus 2 cc. of diluent = 3 cc of 1 100 solution
1 cc. of 1 100 solution plus 9 cc of diluent = 10 cc of 1 1000 solution
1 cc of 1 1000 solution plus 9 cc of diluent = 10 cc of 1 10 000 solution

Feathers

Feathers are obtained directly from the fowl care being taken that no blood or water comes in contact with the feathers One part by weight of feathers is added to five parts by volume of the extracting fluid and placed in the refrigerator for forty eight hours At the end of this time the material is placed in gauze and all possible fluid is squeezed out The fluid is then filtered through a Seitz filter and placed in sterile bottles Cultures can be made in dextrose broth if desired to determine sterility This extract can be used for scratch or cutaneous testing but for intradermal testing it should be diluted ten times with the extracting fluid

Dog Hair Cat Hair Rabbit Hair Horse Hair Goat Hair Cattle Hair Horse Dander Sheep Wool and Camel Hair

The animal is shaved or clipped dry care being taken not to use water The material is washed with carbon tetrachloride and allowed to dry It is weighed and one part by weight is added to five parts by volume of extracting fluid The extraction is carried out in the refrigerator for forty eight hours with occasional stirring and it is then filtered through a Seitz filter It is diluted ten times with extracting fluid for intradermal testing

House Dust

Ordinary dust is obtained from the bedroom and other portions of the house with a vacuum cleaner It should be weighed and washed with carbon tetrachloride before extraction One part by weight of

the dried house dust is added to five parts by volume of extracting fluid and it is allowed to remain in the refrigerator for twenty four hours All the fluid is expressed by squeezing through gauze The extract can be used as is for a scratch test, but for intradermal use it is filtered through a Seitz filter and tested for sterility

Stronger extracts can be made by evaporating down to ⅕ of its volume and dialyzing the extract through fine cellophane

Orris Root

One part of powdered orris root is added to five volumes of ex tracting fluid and placed in a refrigerator for forty-eight hours It is then filtered through a Seitz filter and diluted five times before it can be used for intradermal testing

Cottonseed and Flaxseed

These extracts are prepared from the seed, which is weighed and then macerated with a mortar and pestle or ground in a food chopper One part of ground seeds is added to five parts of extracting fluid and extracted in the refrigerator for forty-eight hours The fluid is squeezed out through gauze by pressure Considerable fat from the seeds is present in this extract and this is removed by shaking in a separatory funnel with three volumes of anhydrous (water free) ether After standing for two hours the fat free portion is drawn off and filtered through a Seitz filter

The cottonseed and flaxseed extracts must be diluted to 1 1000 dilutions before they can be used in intradermal testing and sometimes it is safer to start with dilutions of 1 10 000 or 1 100 000 These extracts are highly antigenic and often cause severe local and systemic reactions in sensitive patients and, therefore, extreme care should be exercised in testing with these substances It is always safest to test with a 1 1000 dilution on a cutaneous test and, if nega tive, an intradermal test may be made with a 1 10 000 dilution

Kapok and Cotton

The fiber is used for extraction and the procedure is the same as with cottonseed and flaxseed, except that it is not necessary to defat with anhydrous ether The extracted material is diluted ten times for scratch testing and twenty times for intradermal testing

Pyrethrum

One part by weight of dried pyrethrum powder is mixed with five parts by volume of extracting fluid It is extracted in the usual way for forty-eight hours and filtered through a Seitz filter Dilute the extract five times for intracutaneous testing

Tobacco

One part by weight of untreated leaves is added to five parts by volume of extracting fluid, and allowed to extract for forty eight hours Dialyze through a cellophane membrane for several washings until all irritants are removed Filter through a Seitz filter For intradermal testing it is diluted twenty times

Tobacco Smoke

The smoke of several cigarettes is suctioned into 30 cc of dextrose solution until no further darkening of the solution occurs This is done by holding a lighted cigarette to the suction tubing which carries the smoke directly through a tube into the solution It is then filtered through a Seitz filter For intradermal testing it is diluted twenty times

Silk

One part by weight of the crude cocoon fiber, or the powdered pupal material is mixed with five parts by volume of extracting fluid It is extracted for forty eight hours and filtered through a Seitz filter For intradermal testing it is diluted twenty times

Cereal Grains (Wheat, Rye, Buckwheat, Barley, Corn, Oats, and Rice)

The grains should be in the natural state and unpolished rice should be used Grind in a coffee mill, or with an ordinary mortar and pestle, add one part by weight to five parts by volume of extracting fluid and extract for forty eight hours in the refrigerator All the liquid is squeezed out through gauze and sterilized by filtering through a Seitz filter The concentrated material is used for scratch testing, and for intradermal testing it is diluted 20 times

MEATS (LAMB PORK, BEEF, CHICKEN, VEAL, AND TURKEY)

Obtain fresh meat and remove all possible connective tissue, grind through a meat grinder, add one part by weight to two parts by volume of extracting fluid, and extract for forty eight hours in the refrigerator Express the fluid portion through gauze by squeezing The fat must be removed by shaking the extract with four volumes of anhydrous (water free) ether in a separatory funnel for at least one hour After the fat is removed, dilute the remaining extract two times with the extracting fluid to prevent jellying Sterilize by passing through a Seitz filter The undiluted extract can be used for scratch testing For intradermal tests it is diluted ten times with the dextrose extracting fluid

JUICY FRUITS (TOMATO, ORANGE GRAPEFRUIT, LEMON, LIME)

Express the juice through a press or orange squeezer Two volumes of juice is mixed with one volume of glycerine Cover the surface with toluol and extract for forty eight hours in the refrigerator Remove the toluol by means of the separatory funnel and sterilize by filtering through a Seitz filter This concentration may be used for scratch testing and, for intradermal testing it is diluted ten times with the dextrose extracting fluid

FRUITS (PEARS, PINEAPPLE, BANANA, APRICOT, APPLE, PEACH, AND PRUNE)

It is important to obtain these fruits fresh and in season The whole fruit is macerated to thoroughly mix solid with liquid portions One part by weight is added to one part by volume of glycero saline

Stier's solution Glycerine 46 Gm
Sodium chloride 4 Gm
q s ad distilled water 100 cc

Other steps are the same as those described under juicy fruits Dilute ten times with dextrose extracting solution for intradermal testing

BERRIES, CHERRIES, AND GRAPES

Obtain these fruits fresh and crush to thoroughly mix solid and fluid portions Three parts by weight is added to one part by volume

of glycerosaline solution (Stier) Cover the mixture with toluol and extract in refrigerator for forty eight hours Squeeze the mixture through gauze remove the toluol by filtering through a separatory funnel and sterilize by passing through a Seitz filter Dilute ten times with dextrose extracting fluid for intradermal testing

Yeast

Prepare from a cake of Fleischmann s yeast Defat with anhydrous ether two volumes ether to one part yeast then place in jar twelve hours Then expose to air to drive off fumes Add one part by weight of dried defatted yeast to five parts volume of dextrose extracting fluid Extract in refrigerator for forty-eight hours Pass through Seitz filter and dilute for intradermal testing to 1 200

Dates Figs Prunes

Add one part by weight to five parts volume of glycerosaline Extract for forty eight hours Pass through Seitz filter and dilute ten times for intradermal testing

Condiments (Vanilla Red Pepper Green Pepper Mustard Ginger)

Obtain in dried state and grind finely one part by weight is added to five parts by volume of dextrose solution Extract forty eight hours Dialyze in a cellophane bag several times until all irritants are removed Seitz filter and dilute at least twenty times for intradermal testing

Black Pepper

Use ordinary black pepper Add one part by weight to five parts by volume of dextrose solution Dialyze as with condiments after extracting in refrigerator for 48 hours Seitz filter Dilute at least twenty times for intradermal testing

Caraway Seed

Add one part by weight to five parts by volume of dextrose solution Follow procedure as with condiments Dilute twenty times for intradermal testing

Fish and Sea Food

Same as for meat, except add only one part fish to five parts dex trose fluid Defat with anhydrous ether Filter through Seitz filter. Dilute to 1 200

Olives, Green and Black

Crush and defat with anhydrous ether Add equal parts ground olive to detrose extracting fluid Allow to remain for forty eight hours Filter through Seitz filter and dilute twenty times for skin testing

Avocado Pear

First defat, then extract the same as with solid fruits, using one part by weight to five parts by volume of glycerosaline solution Ex tract for forty eight hours Then Seitz filter and dilute ten times for intradermal testing

Glue

Add one part by weight of solid glue to twenty five parts by volume of dextrose solution Extract for forty eight hours Dilute twice after extraction, and filter through a Seitz filter Scratch tests are made with a 1 1000 dilution and intradermal tests with a 1 10,000 dilution

Gums (Tragacanth, Acacia Karaya)

Heat in water bath for one hour at 60° C (140° F) for three consecutive days Add one part to one hundred parts dextrose solution Extract for forty eight hours Seitz filter and use as is for testing

Hops

Add one part by weight to five parts dextrose solution Extract for forty eight hours Seitz filter and dilute twenty times for testing

Dill

Add one part by weight to five parts dextrose solution Extract for forty eight hours then dialyze as with condiments Seitz filter and dilute twenty times for skin test

Casein

Add one part by weight to 50 cc glycerosaline solution Extract forty eight hours Seitz filter and dilute to 1 100 for skin testing

Cheeses

Add one part to five parts of dextrose solution Extract for forty eight hours Seitz filter and dilute twenty times for skin testing

Leafy Vegetables (Lettuce Okra String Beans Spinach Cauliflower Cabbage Asparagus and Turnip)

Grind the fresh vegetable in a food grinder mix the solid and watery portions and add one part by weight to one part by volume of glycerosaline solution It is not necessary to add toluol The same steps are followed out as for the other foods described above

Peas and Beans

The untreated seed is purchased and after grinding to a fine meal, one part by weight is added to three parts by volume of dextrose extracting fluid Express the juice by squeezing through gauze and defat with anhydrous ether Additional steps are the same as for the other foods Dilute ten times for intradermal testing

Potatoes Carrots Onions Sweet Potatoes and Beets

Peel and grind in a food grinder add one part by weight to one part by volume of dextrose extracting fluid and extract in refrigerator for forty-eight hours Sterilize by filtering through a Seitz filter Dilute ten times for intradermal testing

All Nuts (Peanuts Almonds Walnuts Pecans Etc)

Remove the shells and grind the kernels Add one part by weight to two parts by volume of dextrose extracting fluid and extract for forty eight hours Defat with anhydrous ether the same as described for meats Dilute ten times for intradermal testing

Milk

Fresh skimmed milk (800 cc) is used and the casein is removed by adding a junket tablet or 2 5 cc of 1 per cent rennin Place in an

incubator at 37° C for thirty minutes caution being exercised not to stir the mixture The clabber which contains the casein is re moved by filtering through gauze and then through filter paper The filtrate contains the lactalbumin which must be precipitated from the whey by adding three volumes of acetone to it and then placing it in a refrigerator for twenty four hours Pour off the supernatant fluid and discard it Centrifuge the remaining filtrate and wash it with acetone several times and dry it in the incubator One weight of the dried powder is mixed with fifty parts of glycerosaline solution (Stier) and extracted for forty eight hours The remaining steps are the same as for the other foods described For intradermal testing dilute it twenty times

Eggs

Separate the egg yolk and the egg white The yolk is mixed and stirred with ten parts by volume of the dextrose extracting fluid and extracted for forty eight hours Defat with anhydrous ether and sterilize by filtering through a Seitz filter Dilute twenty times with the extracting fluid for intradermal testing

Egg white is diluted ten times with the dextrose extracting fluid and allowed to extract for forty eight hours in the refrigerator Sterilize it by filtering through a Seitz filter Dilute ten times for intradermal testing

Coffee Cocoa and Tea

Grind the bean or tea leaves in a coffee mill and mix one part by weight to five parts by volume of the dextrose extracting fluid The other steps are the same as those described for peas and beans Dilute ten times for intradermal testing

Oil Extracts (Poison Ivy [Rhus Toxicodendron])

Fill a pint jar with the ivy leaf Inexpensive rubber gloves and scissors should be used in handling the ivy because they should be thrown away after handling

Saturate the leaves with anhydrous ether (water free) cover jar tightly and allow to remain for forty eight hours Pour the liquid into a dish and allow it to evaporate Corn oil which has been steril

ized in the autoclave, is added in the proportion of one part oil resin to five parts corn oil and this is the stock solution For patch testing it is diluted 1-25

ALL OTHER OILS

Sufficient acetone U S P is added to the material (leaves) to cover the leaves in a jar, which is then tightly covered and allowed to remain at room temperature for forty eight hours Shake the jar gently several times during this period Pour the liquid into an evaporating dish and eliminate the acetone fumes by directly blowing on it with an electric fan A very viscid resin remaining is the oil extract Almond oil, which has been sterilized in the autoclave, is added to the oil residue in sufficient amount to the point of complete solution Solution is aided by very gentle heating Dilute this material ten times with sterile almond oil for patch testing

BACTERIAL FILTRATE

1 Inoculate 200 cc of glucose broth with a loopful of a pure culture of the organism

2 Incubate at 37° C for six days

3 Add 1 cc of melted phenol, drop by drop with continual shaking This makes 0 5 per cent solution of phenol

4 Place in the refrigerator overnight, pass through a sterile Seitz filter, and transfer to sterile vaccine bottles

Test for sterility

1 After standing three or four days, remove 0 2 cc with a sterile needle and syringe and place in thioglycollate glucose broth

2 Incubate for seventy two hours and if there is no growth the filtrate may be used

3 If growth appears, the filtrate must be discarded and a new one prepared

APPENDIX

Appendix 1

Hay Fever Plants and Their Locations in the United States

Trees

The trees listed below are found widely distributed over all parts of the United States

Elm	Oak
Maple	Willow
Poplar (cottonwood)	Box Elder
Ash	Hickory
Hazelnut	Tree of Heaven
Sycamore	Birch

In addition the following trees are responsible for hay fever in the localities specified

The *paper mulberry tree* is found throughout the eastern states, both in the northern and southern parts

The *mountain cedar tree* grows in southern Texas.

The *mesquite tree* is found in various parts of Texas

The *black walnut tree* causes a rather severe type of spring hay fever in California

The *olive tree* also causes hay fever in California

The *black spruce tree* grows in the northern states Many patients are sensitive to the dried needles of this tree, developing hay fever symptoms during the Christmas season when exposed to this common type of Christmas tree

The trees cause hay fever during the months of February, March, and April. In some localities, particularly the northern states where the trees pollinate at a later date, symptoms of hay fever may be present even as late as May.

Grass Group

June grass, or *blue grass*, is found almost everywhere in the United States except in Georgia, Texas, and Miami, Florida

Timothy orchard grass and *red top* have the same distributions as blue grass

Bermuda grass and *Johnson grass* are found principally in the southern states including Florida Georgia Louisiana Texas Alabama Tennessee and as far north as Louisville Kentucky

Sweet vernal grass is found principally in Baltimore Boston New York Philadelphia and Pittsburgh

Ragweed Group

Short ragweed and *giant ragweed* are found everywhere in the United States with the exception of the following cities Boise Idaho Portland Oregon Salt Lake City Utah San Antonio Texas

Western ragweed grows in Illinois Idaho Texas Colorado and throughout the western states

Southern ragweed is found in the states south of Missouri

Cocklebur is found throughout the United States

Burweed marsh elder is particularly common throughout Illinois and other midwestern states

False ragweed is found in Idaho Colorado and Utah

Slender false ragweed is found principally around San Antonio Texas

Marsh elder grows in some midwestern regions

Goosefoot Group

Lamb s quarters is found in every region of the United States

Russian thistle grows in the northern part of the United States and is rarely found in the southern states

Carelessweed Group

Pigweed is found widely distributed throughout the United States

Western water hemp is found in the western and southwestern states

Spiny amaranth is found in the southwestern states

Wormwood Group

Annual sage is found in parts of the South and Southwest

Sage brush grows mainly in Idaho and Utah but is found in many other western states

Biennial sage is found in the midwestern states

Prairie sage grows in Salt Lake City and Utah

Miscellaneous

Red sorrel grows in the northern eastern and western states but not south of Kentucky

Hemp grows in Missouri Nebraska and Arkansas

English plantain is found throughout the United States except for the extreme southern part

Yellow dock is common throughout some southern states

The grasses cause symptoms of hay fever from the middle of May until the middle of July The ragweed goosefoot and wormwood groups produce symptoms from about August 1 until November 1

Hay Fever Plants
Outside the United States

Alberta has very little pollen but cocklebur and Russian thistle are the most important hay fever plants

In central and eastern *British Columbia* sagebrush is common

Ontario especially the southern end has the identical pollen distribution of Michigan and New York states The trees grasses and weeds are the same as in our great lakes area

Quebec and *Montreal* have ragweed pollen that compares with Vermont and New York

Mexico City has very little ragweed pollen Ash oak and cedar tree pollens are abundant Bermuda grass is quite common in Mexico City and the surrounding area June grass and timothy are also common

Cuba and *Puerto Rico* have no ragweed pollen but sugar cane and Bermuda grass are abundant

Bermuda has no grass or ragweed problem but Gay reports large quantities of cedar pollen in the air in March

Appendix 2

POLLEN RECORDS FOR 1949 IN POLLEN GRAINS PER CUBIC YARD

Arranged Alphabetically by States

CALIFORNIA Los Angeles[4]

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Alder	11	11											22
Elm		3	6										9
Walnut		2	2	72	9	1							86
Cypress		10	30	28	8								76
Acacia		3	6	1			2				4		16
Sycamore			18	18									36
Oak			2	62	10								74
Olive				9	99	36							144
Grass	4	2	12	16	62	36	24	20	26	16	12	2	232
Chenopodium			2	3	10	12	15	19	12	9	3		85
Sage	4						4	14	16	24	8		70
Ragweed				9	7	2	3	7	18	11	5		62

Pasadena[5]

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Oak			9	268	75	11	1						364
Olive				2	158	108	6						274
Walnut			4	90	22	7	4						127
Cottonwood			14										14
Elm			8						64	36	3		111
Sycamore				108	8								116
Eucalyptus	10	3	10	54	2	15				2	3	7	106
Alder	25	15	15										55
Acacia	1	7	9	15	1	8		2					43
Deodar									3	98	9		110
Palm				5		3				8		3	19
Grass	10	3	36	172	134	110	84	65	36	37	60	25	772
Chenopodium			4	10	4	12	16	55	15	15			131
Plantain							1	3					4
Sage	5	1					1	14	9	27	29	16	102
Ragweed							2	4	28	21	13		68
Miscellaneous	28	65	161	189	184	154	72	74	93	77	69	46	1212

COLORADO Glenwood Springs[1]

(June - September)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Oak						54							54
Cedar						3							3
Plantain						12							12
Grass						90	12	2					104
Russian thistle						2	5	13					20
Kochia								3	3				6
Other chenopods						16		8	2				26
Sagebrush								13	192				205
Composite									4				4
Ragweed						3		50	18				71
Miscellaneous						54	6		10				70

DISTRICT OF COLUMBIA Washington[11]

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Juniper	11	88	49		8								156
Elm		250	92										342
Maple		6	46	255	269	6							582
Alder		46		2									48
Poplar		2	54	90									146
Birch		6	12	116	70								204
Willow			4	50									54
Oak				1043	16								1059
Hickory				8	68	1							77
Beech				6	56	1							63
Ash				107									107
Paper mulberry				2520									2520
Sycamore				1241	3	6	6						1256
Linden				8	49								57
Walnut				10	12								22
Sweet gum				39	3	3							45
Grass				4	130	104	14	27	64	23			366
Plantain					40	138	26	24	3	4			235
Red sorrel				3	146	20							169
Red mulberry				42	90	3							135
Tree of heaven					61	94							155
Composite						4		7	16	6			33
Chenopodium							2	8	22	2			34
Ragweed								610	1537	39			2186
Miscellaneous		4	28	650	362	108	26	16	34	11			1239

FLORIDA Key West[1]

(June November)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Grass						20	61	63	29	49	2		224
Chenopodium						1	7	2	1	5			16
Magnolia						2		3					5
Sedge							2						2
Composite							9	1		3	1		14
Ragweed						2	5	9	4				20
Miscellaneous						9	124	8	27	11	1		180

Miami Beach[12]

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Australian pine		272	74	81	5	2							434
Grass	3	15	5	45	37	35	10	14	13	8	7	11	203
Amaranth		2			2	1	1		1				7
Ragweed					49	31	20	12	1	1	80		194

Orlando[13]

(Sept 1 1948 Sept 1 1949)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Grass	74	46	398	358	306	166	114	130	92	44	48	56	1832
Oak	10											15	25
Alder	2	20							8				30
Magnolia									10				10
Ragweed							22	133	266	50			471
Miscellaneous									56			4	60

NEW MEXICO Albuquerque[32]

(February December)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Elm		4817	3460										8277
Juniper		3	2376	190	25								2594
Poplar			1735	2690	13								4438
Oak				46	30								76
Tamarisk				303	92								395
Grass					290	186	160	196	10				842
Russian thistle					7	197	443	340	84	12		3	1086
Kochia								140	109	9			258
Composite							168	188	36	12			404
Ragweed								241	421	126	4		792
Miscellaneous			28	40	110	38	16	74	54	8	2	16	386

NEW YORK Garden City[36]

(March - September)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Maple			136	56									192
Birch			2	747	250	1							1000
Poplar			1	11									12
Ash			1	137	12								150
Sweet gum				6	1								7
Willow				11	20								31
Elm				38									38
Beech				1	65								66
Hickory				2	2	1							5
Sycamore				29	107	7							143
Black walnut				3	4								7
Oak				586	1069	3							1658
Grass				10	144	184	63	12	83				496
Plantain				1	56	75	29	18	8				187
Dock					32	67							99
Linden						5	2						7
Composite						2	1						3
Chenopodium							3	19	11				33
Ragweed								433	1565				1998
Miscellaneous					1								1

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
NORTH CAROLINA Charlotte[38] (January - October)													
Cedar	162	47											209
Alder	206	9											215
Elm	75	301	16										392
Oak		8	441	1500	107								2056
Walnut			62	60	7								129
Hickory			118	99	1								218
Pecan			75	133	89								297
Ash				42									42
Willow				5									5
Grass			22	112	78	94	10	22	66	14			418
English plantain					2	40	11	2	6				61
Ragweed								364	1786	18			2168
OREGON Portland[46]													
Hazel		136	236										372
Willow		14	20	32									66
Cedar		242	927	66	14								1249
Elm			270	48	3								321
Alder			1065	816	15	2							1898
Birch				93	4								97
Poplar			2	40									42
Maple				78	15								93
Ash				46	23								69
Oak				2	28	2							32
English walnut				3	48								51
Grass				28	150	486	140		40	10			854
Plantain			13		26	96	111		23	21			290
Chenopodium			15	2	16	68	27		9	14			151
Composite					2								2
Sedge						6							6
Ragweed						4	7		7	4			22
Sage									2	4			6
Miscellaneous				4	10	18	2				2		36
RHODE ISLAND Providence[50] (May - October)													
Birch					422								422
Oak					931	6							937
Ash					69								69
Maple					42								42
Elm					5								5
Grass					224	390	94	12	16				736
Ragweed								575	834	12			1421

UTAH Salt Lake City[53]
(April September)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Alder				79									79
Juniper				57									57
Poplar				612	27								639
Box elder				1248	148								1396
Birch				6	4								10
Willow				22	4								26
Wingscale				20	51	79	46						196
Grass					74	94	82	16	4				270
Greasewood					15	2							17
Scrub oak					75	20							95
English plantain						26	19	4	2				51
Ragweed						4	14	150	305				473
Tree of heaven						4	4						8
Russian thistle							131	118	22				271
Kochia							2	234	28				264
Sugar beet								70					70
Sage								48	386				434
Composite								2	2				4
Pigweed								7	10				17
Miscellaneous				18	26	34	12	28	12				130

WISCONSIN Milwaukee[56]
(April October)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Willow				10									10
Maple				116									116
Box elder				8	488								496
Elm				543	134								677
Hickory				3	34	10							47
Birch				2	23								25
Ash					31								31
Oak					258								258
Grass					10	708	194						912
Dandelion					2	2							4
Miscellaneous							2						2
Plantain								4					4
Ragweed								1722	1949	7			3678

MANITOBA Winnipeg[57]
(April October)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Alder				12									12
Poplar				48									48
Elm				905	3								908
Hazel				12									12
Maple				150	54								204
Willow				6	4								10
Ash				2	14								16
Birch					25								25
Oak					132	3		1					136
Grass						20	38	12	8				78
Mustard						19	2						21
Chenopodium							28	65	11				104
Ragweed								216	54	4			274
Sage								15	6				21
Miscellaneous					1	2	10		2				15

MEXICO Mexico City[63]
(January October)

	JAN	FEB	MAR	APR	MAY	JUNE	JULY	AUG	SEPT	OCT	NOV	DEC	TOTAL
Ash	838	3051	497	6						15			4407
Cedar	426	564	347	41	104	82		47	69	176			1856
Alder	397	391	210	33	11								1042
Oak		91	607	125	33								856
Grass			22	46	66	152	208	218	22	12			746
Composite				18	30					46			94
Amaranth						12	2	29	12				55
Ragweed							4	194	334	36			568

State and City	Pollen grains per cu yd of air: Annual totals 1946	1947	1948	1949	Maximum count 1949	Apex date 1949	Average ragweed index
ARIZONA							
Grand Canyon National Park[1]							
North Rim (fall only)			20				0 15
South Rim (fall only)		16					0 12
Phoenix (fall only)[2]		29					0 21
ARKANSAS							
Little Rock[3]		3450	4679				63 0
CALIFORNIA							
Lassen Volcanic National Park[1]		3					0 03
Los Angeles[4]		60	119	62	1	9/22	0 51
Monterey[64]				46	1	6/4	0 24
Pasadena[5]		122		68	9	11/14	0 87
Sequoia National Park[1]		3					0 03
Yosemite National Park[1]		50					0 29
COLORADO							
Colorado Springs[6]		1324	1104				27 0
Glenwood Springs[1]				68	14	8/25	0 78
Mesa Verde National Park[1]			97				0 52
CONNECTICUT							
Bridgeport[7]			1633	1724	181	9/6	31 0
Fairfield[7]			1391				26 0
Hartford[8]			3321	3159	510	9/2	54 0
New Haven[9]	1906	856	1354	876	97	9/7	23 0
Stratford[7]			1222				26 0
Waterbury[10]	389	1048	781	1181	112	9/1	19 0
DISTRICT OF COLUMBIA							
Washington[11]	2158	2108	2330	2186	220	9/1	39 0
Washington Airport[11]			2154				35 0
FLORIDA							
Everglades National Park[1]							4 0
Key West[1]				20	2		0 12
Miami Beach[12]			88	194	7	5/28	0 86
Orlando[13]				471	36	9/28	6 0
GEORGIA							
Atlanta[14]		1420	1584				30 0
ILLINOIS							
Chicago[15]	4116	7526	4017	8067	583	9/4	70 0
Decatur[16]		9660					114 0
Peoria[17]		13071	10324				108 0
Rockford[18]		9471	6569	11083	814	8/30	91 0
INDIANA							
Evansville[19]				12356	947	9/7	111 0

State and City	Pollen grains per cu yd of air: Annual totals 1946	1947	1948	1949	Maximum count 1949	Apex date 1949	Average ragweed index
INDIANA (Continued)							
Indianapolis[20]		6655	7591	13633	1102	8/24	121 0
IOWA							
Iowa City[21]	10178	13046	8851	4626	415	8/31	97 0
KANSAS							
Goodland[1]		731					23 0
KENTUCKY							
Trappist[22]				7846	885	9/5	86 0
MAINE							
Orono[23]				614	169	8/28	14 0
MARYLAND							
Bethesda[11]			5755				65 0
MICHIGAN							
Ann Arbor[24]		13758	12258	11002	1116	9/2	116 0
Detroit[25]		4989	3067	5144	417	8/27	66 0
MINNESOTA							
Minneapolis[26]				24473	2574	8/24	200 0
MISSOURI							
St Louis[27]				13489	1112	8/19	124 0
MONTANA							
Glacier National Park[1]							
Belton	11	11					0 10
Many Glacier	9	9					0 07
NEBRASKA							
Omaha[28]		12207	9307				90 0
NEVADA							
Lake Mead[1]		389					4 0
NEW HAMPSHIRE							
Bath			185	169	54	8/28	3 0
Berlin		274	1119	288	32	9/1	11 0
Bethlehem				209	47	8/28	6 0
Carrol				54	14	8/26	0 41
Charlestown			540	828	241	9/2	14 0
Colebrook		15	79	61	22	9/7	2 0
Concord		264	208	500	90	8/27	7 0
Conway				299	54	8/26	6 0
Dixville				126	36	9/5	3 0
Errol			46	112	22	8/27	0 62
Exeter		329	2069	1278	256	9/2	17 0
Groveton			135	245	47	9/4	2 0
Hillsboro			189	331	122	8/29	5 0
Hinsdale			328	738	86	9/5	11 0

State and City	Pollen grains per cu yd of air					Apex date 1949	Average ragweed index
	Annual totals				Maximum count 1949		
	1946	1947	1948	1949			
NEW HAMPSHIRE (Continued)							
Holderness				230	47	8/28	5 0
Keene		220	585	382	47	9/3	8 0
Laconia		29	1073	198	58	9/1	12 0
Lancaster				115	18	9/1	0 75
Lebanon		4	1797	918	176	8/30	17 0
Lincoln			217	193	61	8/27	3 0
Littleton				86	22	8/28	2 0
Manchester			501	644	101	8/28	11 0
Moosilauke				68	11	9/1	0 45
Nashua		137	2542	2927	464	9/2	28 0
New Ipswich			360	580	148	8/19	9 0
New London		0	177	677	140	9/1	6 0
North Conway		32	300				4 0
Ossipee			112	173	32	8/28	3 0
Pittsburg			87	191	32	8/27	3 0
Plymouth			201				4 0
Rochester			809	788	79	9/4	17 0
Rye			590	810	83	9/3	15 0
Warren		47	137	194	58	9/7	2 0
Weirs				371	50	9/11	9 0
Whitefield			90	230	29	8/27	2 0
NEW JERSEY							
Dover[30]			1167				21 0
Freehold[30]			6126				72 0
Maplewood[30]		1998	1003	1129	161	9/1	21 0
Marlboro[30]				3129	473	9/1	40 0
New Brunswick[30]		830	7036	4360	607	9/1	74 0
Pitman[31]		3995					51 0
Sandy Hook[30]			1719				39 0
Teaneck[30]		1809					31 0
Verona[30]	944	1306	1710	2180	278	9/1	33 0
Westwood[30]			839				18 0
NEW MEXICO							
Albuquerque[32]		97	674	792	90		9 0
NEW YORK							
Albany[33]	2250	2374	2282	4586	366		45 0
Ausable Forks[33]			872				20 0
Big Indian[33]				216	36		3 0
Big Moose[33]	260	242	296	510	68		6 0
Bronx[30]	1203	1121		1082	196	9/1	25 0
Brooklyn[30]	853	1043		1258	331	9/1	25 0
Buffalo[34]	4994	4576	3261	3522	396	9/4	56 0
Croton[30]	1163	1728					29 0
East Berne[33]			1604				32 0
Elmere[33]							49 0

State and City	Pollen grains per cu yd of air: Annual totals 1946	1947	1948	1949	Maximum count 1949	Apex date 1949	Average ragweed index
NEW YORK (Continued)							
Fire Island[33]		*1072*					*23.0*
Fleischmanns[33]				466	124		7.0
Flushing[35]	900	1865	1285	1934	266	9/1	29.0
Garden City[36]		1198	1437	1998	458	9/1	31.0
Hague[33]	856	612	80	774	480		16.0
Haines Falls[33]							5.0
Hunter[33]			572	3464	370		29.0
Indian Lake[33]		*358*	*226*	*630*	*80*		*7.0*
Jamaica[30]		1596					35.0
Jamestown[33]	5616						64.0
Keene[33]				444	56		8.0
Keene Valley[33]		78	158	254	32		1.0
Keesville[33]				1380	114		26.0
Lake George[33]				*1238*	*148*		*23.0*
Lake Kushaqua[33]				982	144		18.0
Lake Placid[33]	292		414	764	104		10.0
Liberty[33]				1310	128		25.0
Long Lake[33]	206	218	278	390	68		4.0
Loon Lake[33]			204				5.0
Lowville[33]							20.0
Manhattan[30]	1327	1808		1497	205	9/4	26.0
McKeever[33]		126	610	908	106		10.0
Minnewaska[33]				777	282		22.0
New York Metropolitan Ave[30]	*1217*	*1564*	*1911*	*1991*	*360*	*9/1*	*34.0*
North Creek[33]	1164	968	630	1654	146		20.0
Northville[33]			746	2250	332		27.0
Old Forge[33]				704	112		16.0
Paul Smiths[33]			300	308	74		6.0
Phoenicia[33]			2116	388	34		20.0
Pine Hill[33]	340	396	378	236	28		6.0
Plattsburg[33]	1934	2636					41.0
Pomona[33]				1770	172		30.0
Port Henry[33]			746				14.0
Raquette Lake[33]				*526*	*94*		*9.0*
Remsen[33]	956	23362	1202	1974	236		40.0
Rochester[37]	2172	2396	1558	5725	593	8/30	47.0
Rockaway[30]		1515		3274	800	9/1	43.0
Saranac Lake[33]			802	1138	170		19.0
Shroon Lake (Severence)[33]		*290*	*154*	*448*	*54*		*6.0*
Speculator[33]	790	68	366	850	114		9.0
Staten Island[30]	1350	1906		2366	321	9/1	36.0
Tannersville[33]	356	294	324				5.0
Tupper Lake[33]		428	352	602	58		8.0
Wanakena[33]	376	404	278	692	58		7.0
White Plains[30]		1090	1426	1425	244	9/1	27.0
Windham[33]	1722	46	2782	1880	180		28.0
Zena[33]		484	788	610	78		12.0

State and City	Pollen grains per cu yd of air						
	Annual totals				Maximum count 1949	Apex date 1949	Average ragweed index
	1946	1947	1948	1949			
NORTH CAROLINA							
Charlotte[38]		3592	1975	2168	198	9/1	44.0
OHIO							
Akron[39]	10011	8772	7030	12538	1317	9/5	99.0
Cincinnati[40]				12134	1181	9/2	109.0
Cleveland[41]	5483	4035	5385	6599	457	9/1	66.0
Columbus[42]				6910	685	8/28	75.0
Dayton[43]				9361	857	9/4	92.0
Toledo[44]	11475	14307	12613	19460	1570	8/27	136.0
Youngstown[45]	*4741*	*5063*	*4511*	*7211*	*738*	*9/2*	*69.0*
OREGON							
Crater Lake National Park[1]		7					0.07
Portland[46]				6	1		0.05
PENNSYLVANIA							
Broomal[31]		2208					40.0
Hatboro[31]		3560					48.0
McKeesport[47]				12455	928	9/1	117.0
Meadville[48]				5690	460	9/2	70.0
Philadelphia[31]	3830	2549	3177	4036	343	8/29	54.0
Pittsburgh[49]	6600	3449	7619	17328	1249	9/2	93.0
RHODE ISLAND							
Providence[50]		1162	1045	1421	144	9/1	28.0
TENNESSEE							
Great Smoky Mts National Park[1]							
Headquarters		582					13.0
Newfound Gap		204					4.0
Nashville[51]	9470	4488	6168	7213	688	9/6	70.0
TEXAS							
Dallas[52]	13523	21810	25543	20338	832	9/23	154.0
UTAH							
Bryce Canyon National Park[1]			148				0.88
Salt Lake City[53]		913	459	473	40	9/9	10.0
Zion National Park[1]		56	169				0.68
VERMONT							
Burlington[54]			3700	2264	131	9/4	49.0
VIRGINIA							
Shenandoah National Park[1]							
Headquarters			2165				35.0
Big Meadows			638				10.0
WASHINGTON							
Olympic National Park[1]							
Headquarters (Elwha)		4	7				0.09
Hurricane Ridge			7				0.09

State and City	Pollen grains per cu yd of air						Average ragweed index
	Annual totals				Maximum count	Apex date	
	1946	1947	1948	1949	1949	1949	
WISCONSIN							
Madison[55]	4620	14946	4725	5387	620	8/28	87 0
Milwaukee[56]	9916	11656	6688	3678	1656	9/1	93 0
WYOMING							
Grand Teton National Park[1]			14				0 11
MANITOBA							
Winnipeg[57]		492	701	274	50	8/21	8 0
ONTARIO							
Hamilton[58]	5772	12618	4688	6876	1109	9/5	84 0
QUEBEC							
Montreal (Mitchell)[59]			1353	3086	274	8/27	32 0
Montreal (Cabana)[60]				2537	288	8/27	40 0
Montreal (Rose)[61]				3323	413	8/27	49 0
CUBA							
Havana[62]		30					0 18
MEXICO							
Mexico City[63]			745	568	36	9/13	14 0

[1] Oren C Durham
[2] Charles W Vivian
[3] Alan G Cazort
[4] Abraham M Tatgow
[5] Willard S Small
[6] William C Service
[7] Eugene H Walzer
[8] Rose H Klein and George Horwitz
[9] Barnett P Freedman
[10] Sidney W Jennes
[11] Eloise W Kailin
[12] Lewis Fakey
[13] Clarence Bernstein and Ronald J Mann
[14] John L Jacobs
[15] Theodore B Bernstein
[16] Helen C Hayden
[17] Leonard H Harris
[18] Nordahl O Gunderson
[19] Herbert S Dieckmann
[20] Bennett Kraft and C B Bohner
[21] Ronald Rooks
[22] A J Pelly
[23] Martyn A Vickers
[24] John M Sheldon
[25] Sidney Friedlaender and Alex S Friedlaender
[26] A Orville Dahl
[27] Mary C Johnson
[28] Ernest L MacQuiddy
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[30] Matthew Walzer Robert A Chait Jerome Sherman Richard Wiseman Israel Glazer
[31] George I Blumstein and Jay Spiegelman
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[34] Carl E Arbesman
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[36] Roland T Jeffery
[37] Jerome Glaser
[38] Lester C Todd
[39] Karl D Way
[40] John S Wiley
[41] Harold J Friedman
[42] Gareth E Gilbert
[43] S William Simon
[44] Karl D Figley and R Siegert
[45] Samuel R Zoss
[46] Frank Perlman and Elizabeth C Mackin
[47] P M Menlowe
[48] Luther J King
[49] Leo H Criep T H Aaron and W K Riley
[50] Francis H Chafee
[51] Edna S Pennington
[52] J Harvey Black
[53] Dean A Moffat
[54] Harold E Nedivetsky
[55] William A Mowry and Helen P Davis
[56] Theodore L Squier and Howard J Lee
[57] Charles H A Walton and Margaret G Dudley
[58] Robert F Hughes
[59] Howard S Mitchell
[60] L P Cabana
[61] Bram Rose
[62] Jose N Quintero
[63] Jose L Cortes
[64] Dar D Stofer

APPENDIX 3

Pollination Schedule for Many Important Allergens*

		Pollination dates
A *New England eastern and central states* Maine New Hampshire Vermont Connecticut Rhode Island Massachusetts New York New Jersey Pennsylvania Maryland Washington D C Virginia West Virginia Kentucky Ohio Indiana Illinois Michigan and Wisconsin		
Trees	Beech	April May
	Birch	April May
	Hickory	April May
	Black walnut	March May
	Cottonwood	April May
	White ash	April May
Amaranth group	Spiny amaranth	June September
	Pigweed (red root)	July September
Grasses	Sweet vernal grass	May June
	Orchard Grass	May June
	June grass (blue grass)	May July
	Timothy	June July
	Red top	June July
Plantains	Plantain	May September
Ragweed group	Ragweed short	August October
	Ragweed giant	August October
	Cocklebur	July September
Chenopod group	Lamb s quarters	June September
	Russian thistle	June September
Dock group	Yellow dock	May July
	Sheep sorrel	May July

		Pollination dates
B. Southern states. Georgia, Florida, Alabama, Tennessee, Mississippi, Arkansas, Louisiana, Oklahoma, *Texas*		
Trees	Mountain cedar	December-February
	Cottonwood	February-April
	Black walnut	March-May
	Oak	April-May
	Pecan	April-May
Amaranth group	Spiny amaranth	June-September
	Pigweed (red root)	July-September
Grasses	Sweet vernal grass	April-July
	Orchard grass	April-August
	Perennial rye grass	May-July
	June grass (blue grass)	May September
	Bermuda grass	May-September
	Timothy	June-September
	Red top	June-September
	Johnson grass	June-October
Plantains	*Plantain*	May-September
Ragweed group	Ragweed - short	August-October
	Ragweed - giant	August October
	Cocklebur	July-September
	Marsh elder	August October
Chenopod group	Lamb's quarters	June-September
Dock group	Sheep sorrel	May-July
	Yellow dock	May-July
C *Middle* western states Minnesota, Iowa, Missouri, Kansas, Nebraska, South Dakota, North Dakota		
Trees	Black walnut	March-May
	Cottonwood	March-May
	Oak	April May
	Hickory	April-May
	Beech	April-May
	Birch	April-May
	Summer cypress	July-October
Amaranth group	Spiny amaranth	June-September
	Prostrate pigweed	June September
	Red Root pigweed	June September
	Western water hemp	July-October

		Pollination dates
C *Middle western states (continued)*		
Grasses	Sweet vernal grass	April July
	Orchard grass	April August
	June grass	May September
	Timothy	June August
	Red top	June September
Plantains	Plantain	May September
Ragweed group	Ragweed - short	August October
	Ragweed - giant	August October
	Western ragweed	August October
	Marsh elder	August October
	Cocklebur	July September
Chenopod group	Lamb s quarters	June September
	Russian thistle	July September
	Annual salt bush	July September
Wormwood group	Sage brush	July September
	Green sage	July October
	Pasture sage	July October
Dock group	Sheep sorrel	May July
	Yellow dock	May July
D *Rocky Mountain states* Montana Idaho Wyoming Colorado Utah		
Trees	Black walnut	March May
	Cottonwood	March May
	Shad scale	March June
	Oak	April May
	Hickory	April May
	Beech	April May
	Birch	April May
	Summer cypress	July October
Amaranth group	Red root pigweed	July September
/	Prostrate pigweed	June September
Grasses	Sweet vernal grass	April July
	Orchard grass	April August
	June grass	May September
	Timothy	June August
Plantains	Plantain	May September

		Pollination dates
D Rocky Mountain states (continued)		
Ragweed group	Western ragweed	August October
	Cocklebur	July September
	Ragweed short	August October
	Ragweed giant	August October
	Slender ragweed	September October
	Rabbit brush	April May
Chenopod group	Lamb s quarters	June September
	Russian thistle	July September
	Annual salt bush	July September
Wormwood group	Sage brush	July September
	Mugwort	July October
	Green sage	July October
	Pasture sage	July October
Dock group	Sheep sorrel	May July
	Yellow dock	May July
E Southwestern states Texas New Mexico Arizona California (southern portion)		
Trees	Mountain cedar	December February
	Cottonwood	February April
	Arizona ash	March May
	Shad scale	March June
	Oak	April May
	Hickory	April May
	Summer cypress	July October
	Mesquite	May August
Amaranth group	Prostrate pigweed	June September
	Red Root pigweed	July September
	Careless weed	July October
Grasses	June grass	May September
	Bermuda grass	May September
	Johnson grass	June October
Plantains	Plantain	May September
Ragweed group	Slender ragweed	September October
	Southern ragweed	September October
	Rabbit brush	April May
Chenopod group	Lamb s quarters	June September
	Russian thistle	July September

		Pollination dates
E *Southwestern states (continued)*		
Wormwood group	Sage brush	July September
Dock group	Sheep sorrel	May July
	Yellow dock	May July
F *Pacific states* Washington Oregon Nevada California (northern)		
Trees	Cottonwood	April May
	Black walnut	March May
	Shad scale	March June
	Oak	March June
	Olive	April May
Amaranth group	Red root pigweed	July September
	Annual salt bush	July September
Grasses	Sweet vernal grass	April July
	Orchard grass	April August
	Perennial rye grass	May July
	June grass	May September
	Bermuda grass	May September
	Timothy	June August
	Red top	June September
	Johnson grass	June October
Plantains	Plantain	May September
Ragweed group	Cocklebur	July September
	Western ragweed	August October
	Slender ragweed	September October
	Rabbit brush	April May
Chenopod group	Lamb s quarters	June September
	Russian thistle	July September
Wormwood group	Sage brush	July September
	Mugwort	July October
Dock group	Sheep sorrel	May July
	Yellow dock	May July

* This schedule gives only an approximate idea as to the various pollens found in the United States Some of these pollens are more frequently hay fever offenders than others In some districts the list may be larger than that presented In California where the pollen is abundant and the number of different pollens is great the clinical problem becomes quite complicated The information contained in the schedule was obtained from surveys conducted in various parts of the country to determine the local pollen flora

Reference Leo H Criep *Allergy* Veterans Administration Medical and Hospital Service Bulletin No 29 March 1940

Appendix 4

Common Inhalant, Ingestant, and Contact Allergens and Their Sources

Feathers and animal dander are considered to be important causes of allergic rhinitis and asthma Dander from cats dogs horses cows rabbits and guinea pigs as well as feathers from chickens geese ducks pigeons parrots and canary birds are the most common

Furs made from rabbits skunk beaver mole mink goat or muskrat are important causes of hay fever in furriers and trappers although a dermatitis may result from the dyes used in contact with the skin Less expensive furs are usually altered and sold under different names Feinberg lists the more important furs that are sold under different names

Species	*Sold As*
Hare dyed	Sable or fox
Hare white	Fox
Rabbit white	Ermine
Rabbit white dyed	Chinchilla
Rabbit dyed	Sable
Rabbit sheared and dyed	Seal electric seal Hudson Bay seal muskrat
Muskrat dyed	Mink sable
Muskrat pulled and dyed	Seal Hudson Bay seal Electric seal Red River seal
Mink dyed	Sable
Marmot (woodchuck)	Mink sable skunk
Opossum	Beaver
Goat	Bear leopard
Fitch dyed	Sable
Kid dyed	Lamb
Otter	Sable
Nutria	Seal beaver otter

Horse dander and hair Frequently used for pillows covers blankets furniture stuffing automobile seats carpet pads cushions mattresses lining and padding clothes sacks and bags wigs gloves hats and furs

Goat hair Mohair covers tapestries plush covering in upholstered furniture suits linings gloves socks felt hats dolls hair wigs monkey fur brushes and bedding

Cat hair Carriage robes lynx and civet furs slippers toys and cheaper furs

Dog hair Rugs Chinese rugs cheaper furs and robes

Rabbit hair Dyed furs felt hats lapin fur fur lined gloves angora wool in sweaters collars cuffs scarfs dresses and toys Often advertised as sable seal chinchilla fox hubian seal electric seal or Hudson seal

Feathers Chicken turkey goose duck pigeon parrot canary and feathers of other household birds or pets are found in pillows furniture feather beds hats dress trimmings fans and dusters

Sheep wool May cause symptoms when in the raw state as in blankets robes mattresses or furniture and wool used for medical purposes In the finished state as in clothing hats carpets or underwear it is seldom important as a cause of symptoms

Camel hair Jaeger wool sweaters portieres shawls alpaca carriage robes muffs coats trimming for coats blankets dress goods hats brushes rugs upholstered furniture and seats in cars

Badger hair Shaving brushes floor brushes

Hog hair Mattresses brushes furniture stiff brushes and toys

Cattle hair Carpet yarns padding under carpets and rugs blankets Chinese rugs mattress and furniture stuffing felt children s toys and doll wigs

Ozite This is a product of animal hairs used as a padding under carpeting and rugs

Cottonseed Symptoms may be produced as an inhalant an ingestant or by direct contact Linters used in mattresses wadding impure cotton cushions comforters upholstery fleece lined underwear waterproofing material artificial silk robes medical and surgical muslin gingham turkish and cotton towels and celluloid will cause the symptoms as will inhalation of fertilizers used on lawns

As an ingestant cottonseed is used in fertilizers flour (as in doughnuts cakes and cookies) French fried potatoes oleomargarine Crisco Spry Wesson Oil Cottolene Snowdrift packing sardines setting olives candles linoleum oil cloth bookbinding setting chocolate soaps mustard and emulsions and liniments for external use For those who are allergic to cottonseed it is best to avoid all canned fish cheap or adulterated olive

oils salad oils salad dressings unless the ingredients are known or made at home pop corn french fried potatoes pie crusts unless made with lard cake mix and gin

*Karaya gum** Used in cathartics drugs certain foods wave sets certain brands of gelatin and junket candies such as gum drops and jelly beans hand lotions hair waving solutions emulsified mineral oils and laxatives diabeti foods as soy bean and almond wafers denture adhesive powder (Dr Wernet s powder Ny Ko denture powder Stix) fillers for lemon pies and custards ices flavors salad dressings and tooth pastes (Lactona and Listerine)

The following laxatives contain Karaya gum Bassaron (Merrell) Karaba (Battle Creek Sanitarium) Imbicoll (Upjohn) Granaya (Squibb) Mucara (Wyeth) and Saraba (Schering)

Silk Broadcloth brocade Canton crepe chiffon crepe de Chine duchess satin foulard faille georgette taffeta jersey plush pongee rugs (oriental) poplin radium silk wash satin tub silk tulle thread uphol stery tapestries velvets silk floss for pillows hosiery lining linit good mufflers

The following substances contain no silk although their names would suggest some silk content Kapok sunfast silk rubberized raincoats Kloster silk Silkatren Rayon Maxwell silk poplin Esskay unequaled best silk subsilk Japsilk

Flax Linen flaxseed and linseed oil obtained from flaxseed poultices Uncle Sam s breakfast" also contains flaxseed and may produce allergic symp toms Flaxseed is used as a meal seed for poultry Linseed is present in linoleum oil silk patent leather printer s ink paint varnishes and furniture polish

Kapok Pillows mattresses life belts upholstered furniture

Glue There are two kinds of glue animal and fish Animal glue is ob tained from the hides of horses cows sheep hogs and rabbits and from the bones and cartilages of sheep calves dogs cats goats cattle and horses Fish glue is made entirely from fishes

Glue is used in cabinet making bookbinding capsules mucilage and paint Where furniture is old dry and loose dry glue may be a factor in causing asthma Allergic symptoms caused by an allergy to glue are most often due to fish glue

Tobacco Tobacco smoke or the tobacco itself may be the cause

Castor bean Castor bean dust

*See Figley K D *Indian Gum (Karaya Gum) Sensitivity* International Correspondence Club of Allergy 7 1937

Orris root Scented face powder, body powders, bath salts, soap, tooth powder, soap powder, cleansing creams, etc.

Pyrethrum Insect powders or sprays, moth powders, incense, etc.

Derris Root Active principle is rotenone used as insecticide and in flea powders

Appendix 5

Ingredients of Some Common Foods

Baking powder Contains sodium bicarbonate cornstarch and frequently egg phosphoric acid aluminum sulphate and tartaric acid

Beef juices prepared Contain meat juice and egg white

Beer ale stout and porter Are usually made from hops and fermented barley malt grain sometimes from wheat rye rice oat and corn

Bologna Contains beef veal pork and spices

Catsup Is made of tomatoes onions spices vinegar sugar green walnuts and thick puree of oysters or other shellfish

Chewing gum Contains chicle latex of the sapodilla tree

Coca Cola Contains caffeine carmel glycerine lime juice phosphoric acid kola nuts essential oils of cinnamon coriander lemon neroli nutmeg and sweet orange

Cocomalt Is made from skimmed milk cocoa sucrose and barley malt

Cooking oil Contains cottonseed oil

Cornflakes Contain corn malt extract sugar and salt

Cream sauce Is made from white sauce and eggs

Farina Contains wheat

French dressing Is made of olive oil salt pepper vinegar and spices

Gelatin Is made of beef veal or pork hides

Gin Contains spirits distilled from wheat barley malt rye or corn Certain of the following extracts may be added an seed caraway seed cardom seed juniper berry cinnamon cloves coriander seed fennel seed calamus root licorice lemon peel orris root sloe berries nutmeg and orange peel

Ginger ale Contains ginger lemon juice and capsium

Grape nuts Are made from wheat barley malt salt and yeast

Hollandaise Is made from eggs butter and lemon juice

Ice cream Contains egg milk and flavors In cheap ice cream cornstarch is substituted for egg

Ices Contain fruit egg and flavoring

Jello Is made from beef gelatine

Junkets Contain milk rennet vanilla cinnamon or nutmeg

Liver sausage Contains pork onions and pistachio

Macaroni Contains wheat and milk

Macaroons Are made of almond meal cocoanut egg white and sugar

Malted milk Is made from barley malt wheat flour and whole milk

Mayonnaise Contains olive or vegetable oil eggs vinegar and spices

Mellin s food Contains wheat flour and bran malted barley and potassium bicarbonate

Meringue Is made from egg lemon and sugar

Noodles Contain wheat and eggs

Oleomargarine Contains beef fat pork fat and cottonseed oil or corn oil

Pablum Contains wheat meal oatmeal yeast beef bone iron salt and alfalfa

Pancake flour Contains wheat corn rye flour sugar milk salt and baking soda

Post Toasties Are made of hulled white corn grits salt and sugar

Postum Contains wheat bran wheat and molasses

Potato chips prepared Contain cottonseed oil

Pumpernickel Is made of rye graham flour bleached clear flour malt salt and caramel

Root beer Contains root bark and herbs essential oils and yeast

Spaghetti Is made of wheat and milk

Tartar sauce Contains mayonnaise capers olives cucumbers and pickles

Tomato soup canned Contains tomato butter onion sugar salt flour and spices

Tuna fish canned Is packed in cottonseed oil

Vinegar Is made from apple grape malt molasses and corn syrup

White bread Contains wheat flour, sugar, salt, yeast, malt, eggs, vegetable oil, and butter.

Wines Are made from the fermentation product of fruits, usually grapes. Egg white is frequently added

Worcestershire sauce Is made of soy, vinegar lime, onions tamarinds, garlic, fish, red chili, and spices.

Appendix 6

Special Diets and Recipes*

WHEAT FREE DIET

DIET MAY INCLUDE

Beverages	Coffee tea cocoa fruit juices
Breads	Biscuits or bread made without wheat flour such as corn meal or rice flour muffins cornbread potato flour muffins oatmeal muffins Ry Krisp castle bread soy bean muffins
Cereals	Barley barley flour cornflakes cornstarch potato flour rice flour rice flakes cornmeal oatmeal rye flour tapioca rice Puffed Rice Rice Krispies
Desserts	Tapioca gelatin fruits puddings thickened with corn starch instead of flour
Eggs	Prepared in any way Do not add wheat products in any form
Fats	All kinds both cooked and raw
Meat fish poultry	Any kind except when treated with flour or bread crumbs
Milk and milk products	Cream butter cheese ice cream buttermilk
Soups	Chicken and meat broths milk soups thickened with corn starch instead of flour
Vegetables	All kinds both cooked and raw

DO NOT EAT

Any wheat or wheat products such as bread gravy sauces macaroni spaghetti noodles pies cake cookies dumplings matzos

*Rowe Albert H *Elimination Diets And The Patient s Allergies* Lea and Febiger 1944 2nd Ed

Sample Menu

Breakfast	Lunch	Supper
Fruit	Egg or cheese	Broth
Cereal (as listed)	Vegetable	Meat or fish
Eggs	Fruit	Potato
Rice muffin with butter	Cornbread with jelly	Vegetable
Coffee or tea for adult	Milk	Dessert
Milk or cocoa for child		Ry Krisp
		Tea or coffee for adult
		Milk for child

MILK FREE DIET

DIET MAY INCLUDE

Beverages	Coffee tea fruit juices
Bread	Ry Krisp cornbread and any bread made without milk cream or butter
Cereals	All kinds They may be served with fruit juices
Desserts	Fruits gelatin Jello pastry made without milk cream or butter tapioca pudding
Eggs	Prepared in any way without milk cream or butter
Fats	Chicken or goose fat meat fat olive oil and other oils such as Mazola Crisco and oleomargarine made without the addition of milk
Fruits	All kinds both cooked and raw
Meat fish poultry	Any kind
Salad dressing	French or mayonnaise dressing
Soups	Broth or vegetable soups
Vegetables	All kinds both cooked and raw

DO NOT EAT

Milk cream butter buttermilk cheese in any form

Sample Menu

Breakfast	Lunch	Supper
Fruit	Egg or fish	Vegetable soup
Egg	Vegetable	Meat or chicken
Cereal with fruit juice	Fruit	Potato
Bread	Bread	Vegetable
Jelly	Jelly	Vegetable salad with French dressing
Coffee or tea without milk or cream	Tea	Bread
		Fruit gelatin
		Tea

EGG FREE DIET

DIET MAY INCLUDE

Beverages	Coffee tea fruit juices
Breads	White rye or pumpernickel or any other bread made without eggs Be sure that the tops have not been brushed with egg white before baking
Cereals	All kinds both cooked and dry Macaroni spaghetti noodles if made without eggs
Desserts	Gelatin fruits and desserts made at home without eggs such as ices ice cream pastry puddings or prune or apricot whip made with cream
Fats	Vegetable and animal fats
Fruits	All kinds both raw and cooked
Meat fish poultry	Any kind broiled or baked without egg
Milk and milk products	Cream milk buttermilk cheese
Salad dressing	French dressing (oil and vinegar)
Soups	Chicken and meat broth vegetable soup cream soups and clear soups made without egg
Vegetables	All kinds both raw and cooked

DO NOT USE EGGS IN CLEARING COFFEE OR SOUPS DO NOT USE EGGS IN ANY FORM

Sample Menu

Breakfast	*Lunch*	*Supper*
Fruit	Soup	Broth
Cereal	Cheese or fish	Meat or chicken
Bacon	Vegetable	Potato
Bread and butter	Fruit	Vegetable
Coffee or tea	Muffin with butter or jelly	Dessert
Milk or cocoa for child	Tea or milk	Bread with butter
		Tea
		Milk for child

WHEAT EGG AND MILK FREE DIET

DIET MAY INCLUDE

Beverages	Coffee tea fruit juices
Breads	Ry Krisp cornmeal muffins cornbread rice muffins *potato flour muffins barley rice and potato flour* soy bean muffins oatmeal muffins
Cereals	Rice barley hominy cornmeal oatmeal cornflakes Rice Krispies rice flakes Puffed Rice
Desserts	Fruits rice cookies tapioca gelatin Jello marmalade preserves jam

Fats	Chicken or goose fat vegetable oils such as Mazola Crisco Wesson Oil Snowdrift oleomargarine made with out the addition of milk
Fruits	All kinds both cooked and raw
Meat fish poultry	All kinds not prepared with milk cream butter eggs flour or crackers
Soups	Chicken or meat broth vegetable soups
Vegetables	All kinds both cooked and raw

DO NOT EAT

Eggs milk or wheat in any form or products made from them such as gravies sauces pastry cake cookies pie bread macaroni spaghetti noodles cheese cream butter buttermilk mayonnaise dressing or wheat products such as Cream of Wheat Shredded Wheat Ralstons Muffets Farina etc

Sample Menu

Breakfast	*Lunch*	*Supper*
Fruit	Baked rice with tomatoes	Soup
Cereal (as listed) with fruit or fruit juices	Vegetable	Meat or fish
Rice muffin	Cornbread	Potato
Jelly or oleomargarine	Fruit	Vegetable
Coffee or tea	Tea	Ry Krisp
		Jello
		Tea

THE USE OF ELIMINATION DIETS BY ROWE

Elimination diets were first suggested by Rowe in 1928 * and he lists a number of foods which in his experience infrequently produce symptoms of sen sitization The general principle of these diets has been to include foods which allow a well balanced menu and thus prevent any undue loss of weight and strength

These diets can be used when symptoms of probable food allergy are not controlled by excluding foods to which positive skin reactions have occurred *or if skin tests to foods are negative or impossible to perform*

Diets 1 and 2 may be prescribed together or separately If sensitization to cereals as a group is suspected Diet 3 may be used first Diet 4 elimin ates all foods except milk Menus for Diets 1 and 2 together and for Diets 1 2 and 3 separately *follow after the diet lists*

One of the selected diets must be taken for at least ten days or even two or three weeks If relief of symptoms does not occur another diet such as 2 3 or 4 should be tried for a similar period

*Rowe Albert H Food allergy J A M A Nov 24 91 1623 1629 1928

It is imperative to adhere strictly to the prescribed diet Foods which are not specified must not be eaten No breads, cookies, or soups should be used unless every ingredient is known. With relief of symptoms other foods, one to three at a time, may be tried every four to seven days, from the remaining elimination diets Thereafter, other vegetables, fruits, meats spices, and nuts may gradually be added In one to three months milk, egg, and wheat may be tried separately at weekly intervals Foods which cause symptoms must be completely eliminated, sometimes for months or even years

Many patients are sensitive to a food, although their skin tests may not show a positive reaction to the particular food This is especially true in patients who have hives These diets are of considerable help in discovering the food or foods responsible for symptoms of sensitization in these persons

Diet No 1

Rice
Tapioca
Rice biscuit
Lettuce
Spinach
Carrot
Beet
Artichoke
Lamb
Lemon
Grapefruit
Pears
Cane sugar
Wesson oil
Olive oil
Salt
Gelatin
Syrup made of maple sugar or cane sugar or cane sugar flavored with mapleine or maple sugar
Olives

Diet No 2

Corn
Rye
Corn pone
Corn rye muffin
Rye bread
Ry Krisp
Tomato
Squash
Asparagus
Peas
String beans
Chicken
Pineapple
Peaches
Apricot
Prunes
Cane sugar
Mazola oil
Wesson oil
Salt
Karo corn syrup
Gelatin

Diet No 3

Tapioca
White and sweet potato
Lima bean potato bread
Soya bean lima bean bread
Beets
Carrots
Lima beans
String beans
Tomato
Beef
Bacon
Lemon
Grapefruit
Peaches
Apricot
Cane sugar
Olive oil
Wesson oil
Gelatin
Salt
Olives
Maple syrup or syrup made with cane sugar flavored with maple

Diet No 4

Milk-2 to 3 quarts a day
Tapioca cooked with milk and milk sugar also may be taken

Note Wesson (cottonseed) oil is included in all diets With sensitiveness to cottonseed as shown by skin tests, this must be excluded and a cottonseed oil shortening such as Crisco must not be used If sensitiveness to cane sugar is suspected, beet sugar or corn glucose may be used

Breakfast Diets 1 and 2

		Approximate Amounts
Beverage	(a) Grapefruit (fresh) juice or lemonade with sugar as desired	1 glassful
	(b) Pineapple juice	
Cereal	(a) Boiled brown or polished rice or colored cornmeal served with apricot, peach, or prune juice and sugar	1/3 cup rice 3 tsp. juice
	(b) Rice Krispies or cornflakes served with grapefruit juice and sugar, or with apricot, peach, or prune juice or maple syrup	or 3/4 cup flakes
	(c) Cold rice or cornmeal fried in Mazola oil, or bacon or chicken fat, served with maple syrup or Karo corn syrup	
Meat	(a) Bacon (moderately crisp) or	3 slices, or
	(b) Lamb chops, lamb or chicken croquettes	1 medium chop
	(c) Lamb kidney fried with bacon	
Bread	(a) Corn pone (2)	2 muffins
	(b) Corn rice muffin (3)	
	(c) Corn rye muffin (4)	or
	(d) Rice biscuit (5)	
	(e) Rice bread (6)	2 slices toasted
	(f) Rye bread (7)	
	(g) Ry Krisp	
Jams or preserves	(a) Peach or prune jam	2 tbsp.
	(b) Apricot or apricot pineapple jam or preserves	
	(c) Grapefruit and lemon marmalade	
	(d) Pear butter	
Fruit	Sliced or whole grapefruit, canned, fresh, or stewed peaches, apricots, pears, pineapple, or prunes	

Note Choices as indicated by letters are offered in all menus, though more than one may be used if desired.

Lunch and Dinner

Salad	(a) Lettuce with apricot, peach, pear, or pineapple with oil dressing or special mayonnaise	2 halves or slices

	(b) Vegetable salad made of tomato carrots beets asparagus peas string beans or artichokes with oil dressing or special mayonnaise	1/2 cup mixed vegetables 1 tbsp oil or dressing
	(c) Sliced tomato or lettuce tomato with oil dressing	
	(d) Lemon gelatin with grated carrots and crushed pineapple	
Soup	(a) Lamb broth clear or with rice carrot peas string beans as desired	1 cup
	(b) Chicken broth clear or with rice carrot peas string beans as desired	
	(c) Split pea soup	
Meat	*(a) Lamb served as lamb chops roast tongue* or stew made with lamb rice corn carrots peas beets or string beans	*2 medium chops* or
	(b) Chicken boiled roasted fried or stewed May be stuffed with rice or *cornmeal May be rubbed with bacon* if desired	1 broiler or *equivalent*
	(c) Thicken gravy or sauces with rice flour or cornstarch	
Vegetables	(a) Spinach carrots asparagus squash *peas artichokes beets tomatoes*	4 tbsp
Bread	Choice of those in breakfast	
Jams or preserves	Choice of those in breakfast	
Dessert	(a) Fruit as suggested in breakfast	4 tbsp
	(b) Rice fruit pudding	
	(c) Tapioca fruit pudding	
	(d) Corn rice cookie or rice cup cakes	
Beverage	(a) Pineapple juice	
	(b) Grapefruit juice or lemonade with sugar	1 glassful

Note Soups may be made only with ingredients in the prescribed diets Canned soups and those in restaurants and hotels are apt to have wheat egg or other forbidden ingredients

Gravies must be thickened only with prescribed flours Gelatin may be incorporated in salads and desserts if desired

Breakfast Diet I

Beverage	*(a) Grapefruit juice or Lemonade with sugar*	*1 glassful*
	(b) Pear juice flavored with lemon	1 glassful
Cereal	(a) Rice boiled or steamed brown served with pear juice or maple syrup and sugar	½ cup cooked rice 3 tbsp syrup

	(b) Rice flakes or Rice Krispies served with pear juice and sugar or cooked pears	3/4 cup Rice Krispies 4 tbsp juice
	(c) Tapioca cooked in water and flavored with lemon juice, lemon rind, and sugar	1 tbsp. dry tapioca
Meat	Lamb chops or lamb patties	2 medium chops
Bread	(a) Rice biscuits	2 medium biscuits
	(b) Rice bread	
Jams or preserves	(a) Pear butter	2 tbsp
	(b) Lemon or grapefruit marmalade	
Fruit	(a) Grapefruit	1 grapefruit
	(b) Fresh or canned pears	3 halves

Note Corn-sensitive patients often react to corn or glucose which must be excluded even in minute amounts.

Lunch or Dinner Diet I

Salad	(a) Hearts of lettuce Dressing of olive or Wesson oil and white vinegar	½ medium head 1 tbsp. oil
	(b) Vegetable salad of lettuce, carrots, beets, artichoke, and olives as desired with above dressing or eggless mayonnaise	1 cupful mixed vegetables
	(c) Lettuce with grapefruit or pears served with oil and lemon juice dressing	½ grapefruit or 2 halves pears
Soup	Lamb broth clear or with tapioca or rice and carrots as desired	1 cupful
Meat	(a) Lamb served as chops, roast, tongue	2 medium lean chops or their equivalent
	(b) Stew made with lamb, rice, or tapioca, carrots or beets. Thicken gravy with rice flour	
Vegetable	Steamed or boiled rice	½ cup cooked
	Spinach, carrots, beets, or artichokes	4 tbsp.
Bread	Choice of those suggested for breakfast	
Jams or preserves	Choice of those suggested for breakfast	
Dessert	(a) Plain lemon or lime gelatin with pears or grapefruits as desired	
	(b) Winter pears baked with maple syrup or brown sugar	1 large pear
	(c) Rice cookie or cup cakes	1 cup cake
	(d) Puffed rice candy	
	(e) Tapioca fruit pudding	

	(f) Rice fruit pudding	
Beverage	Choice of those suggested for breakfast	1 glassful

Note Pure olive oil and Wesson oil only can be used in Diet 1 Imported oil *is usually adulterated. Wesson oil and Crisco must be excluded if* patient reacts positively to cottonseed

Breakfast Diet 2

Beverage	(a) Pineapple or prune juice	1 glassful
	(b) Apricot, peach, and pineapple juices mixed	1 glassful
	(c) Tomato juice	
Cereal	(a) Cornflakes served with pineapple juice or peaches, apricots, or prunes, and juice and sugar	4 tbsp juice ¾ cup Cornflakes
	(b) Cornmeal mush served with maple or Karo syrup	½ cup cooked cereal
	(c) Cold cornmeal mush fried in Mazola oil or bacon fat served with syrup and bacon	
Meat	(a) Bacon	4 medium strips
	(b) Chicken croquettes	1 croquette
Bread	(a) Corn pone	
	(b) Corn, and rye muffin	2 muffins
	(c) Rye bread	1 or 2 slices toasted
	(d) *Ry Krisp*	2 *Ry Krisp*
Jams or preserves	(a) Pineapple preserves	2 tbsp
	(b) Apricot or peach jam	
	(c) Tomato cooked with sugar	
Fruit	Fresh, cooked, or canned pineapple, peaches, apricots, or prunes	½ to ¾ cup

Lunch or Dinner Diet 2

Salad	(a) Sliced tomato or asparagus with Mazola or Wesson oil and white vinegar or mayonnaise	1 large tomato 6 to 8 stalks asparagus
	(b) Combination vegetable salad with tomatoes, asparagus, peas, and string beans as desired with above dressing	2 tbsp oil 1 cup mixed vegetable
	(c) Combination *fruit salad of pineapple*, peaches, and apricots with special mayonnaise thinned with pineapple juice	1 cup mixed fruits

	(d) Chicken and pineapple salad mixed with special mayonnaise	
Soup	(a) Chicken broth clear or with peas, string beans, or tomato as desired	1 cup
	(b) Split pea soup	
Meat	(a) Chicken, roasted, fried, broiled, or stewed May be brushed with Mazola oil and rolled in cornmeal if desired Serve broiled peaches, apricots, or pineapple with fried or broiled chicken	½ broiler or fryer
	(b) Chicken livers rolled in cornstarch or cornmeal and sautéed in Mazola or Wesson oil	
	(c) Thick slices of tomato fried or broiled in oil or bacon fat served with strips of bacon	
Vegetable	Tomato squash asparagus, peas, string beans corn	4 tbsp
Bread	Choice of those suggested for breakfast	
Jams or preserves	Choice of those suggested for breakfast	
Dessert	(a) Fruits as suggested for breakfast	4 tbsp
	(b) Rye cookies	2 or 3 cookies
	(c) Fruit cornstarch pudding with crushed pineapple	3 tbsp
	(d) Jellied prunes with pineapple	

Breakfast Diet 3

Beverage	(a) Grapefruit juice and lemonade with sugar	1 glassful
	(b) Tomato juice	1 glassful
Cereal Substitute	(a) Tapioca cooked with apricot or peach or flavored with lemon, maple syrup, or carmelized sugar	1 tbsp dry tapioca ½ cup
	(b) Lima bean flakes served with apricot peach, prune, or grapefruit juice and sugar as desired	¾ cup lima bean flakes 4 tbsp juice
Meat	(a) Bacon moderately crisp	4 slices
	(b) Beefsteak, chipped beef, beef patties, or tongue	small steak
	(c) Bacon and hashed brown potatoes	
Bread	(a) Lima bean potato bread	2 slices toasted
	(b) Lima bean soya bean muffins	2 muffins

Jams or preserves	(a) Lemon or grapefruit marmalade	
	(b) Peach or apricot jam	
	(c) Tomato preserves flavored with lemon	
Fruit	(a) Sliced or whole grapefruit	1 grapefruit
	(b) Fresh, stewed, or canned peaches or apricots	4 tbsp
	(c) Sliced tomatoes with sugar	

Lunch or Dinner Diet 3

Salad	(a) Sliced tomato with olive or Wesson oil and lemon juice dressing or sugar	1 large tomato
	(b) Vegetable salad of carrots, lima beans, string beans, olives, or tomatoes as desired with olive or Wesson oil dressing or special mayonnaise	1 cup mixed vegetables
	(c) Fruit salad made of grapefruit, peaches, or apricot with above dressing	½ to ¾ cup of fruit
Soup	(a) Beef bouillon, clear or with carrots, lima beans, or tomato	1 cup
	(b) Lima bean soup flavored with bacon	
Meat	(a) Beefsteak, roast, or tongue	Average liberal serving of meat
	(b) Beef stew with potato, carrot, lima beans, or string beans. Thicken gravy with potato flour	
	(c) Calves or beef liver and bacon	
Vegetable	(a) White or sweet potatoes	1 medium sized potato
	(b) Carrots, lima beans, string beans, tomatoes	
Bread	Choice of those suggested for breakfast	
Jams or preserves	Choice of those suggested for breakfast	
Dessert	(a) Fruits as suggested for breakfast	4 tbsp
	(b) Tapioca fruit pudding	
	(c) Lima bean potato flour cookies or cup cakes frosted with sugar and lemon juice icing	2 cookies or 1 cupcake
Beverage	(a) Grapefruit juice or lemonade with sugar	1 glassful
	(b) Tomato juice	

Chicken Croquettes

1 tbsp oil or chicken fat
2 tbsp cornstarch
½ cup liquid (chicken broth)
¾ cup cooked minced chicken
Salt

Make a sauce of fat cornstarch and liquid Add the other ingredients (cooked cornmeal may be added) Cool shape dip in rye flour or crushed cornflakes Bake in medium oven or fry in deep fat

Rice Biscuits

Made by the Battle Creek Sanitarium

Pear Butter

Select firm ripe pears Peel core and cut into rather small pieces To 2 cups prepared fruit add 1 cup sugar Cook slowly stirring frequently to prevent burning for two hours or until the mixture is quite thick

Rice Fruit Pudding

Sauce
1 cup sugar
2 tbsp rice flour
½ tsp salt
1¼ cup boiling water
1 tsp lemon juice or vanilla

Mix sugar salt and rice flour Add water and cook until thick Remove from stove and add flavoring Add boiled rice and apricots or sliced peaches and serve warm Reserve some sauce to pour over the pudding

Tapioca Fruit Pudding

2 halves peaches sliced
1 tbsp dry tapioca
2 tsp sugar
½ cup peach juice and water

Drain peaches and sprinkle with one tsp sugar Cook tapioca in juice and water until it is clear Add remaining sugar and salt Line a baking dish with peaches Fill with tapioca and bake in a moderate oven for 20 minutes

Rice Cup Cakes

2/3 cup hot water
1½ cup rice flour
2 level tbsp shortening
½ cup sugar
¼ tsp salt
3 level tbsp baking powder
1 tsp vanilla

Pour hot water over half the flour Cream sugar and shortening and add to the above mixture beating well Add the other ingredients mixing well Bake in muffin pans about 20 minutes in a fairly hot oven

Baking powder made by Royal or Schilling Co contains no egg

Rye Rolls

1 cake compressed yeast
½ cup sugar
1 tsp salt
2 cups water (cooler than lukewarm)
1 egg
3 tbsp melted fat
7½ cups rye flour

Combine first five ingredients add half the flour and beat Add shortening Mix in the remainder of the flour with the hands Let rise until double in bulk Punch down Set in icebox closely covered The dough will keep several days but is best up to second or third day After shaping the rolls let them rise 2½ hours bake at 400 degrees hot oven and for longer than ordinary rolls

Rye Popovers

2 eggs
1 cup milk
1 cup rye flour
1 tbsp melted shortening
½ tsp salt

Sift flour and salt add milk and eggs beaten together stir Add shortening and beat long and vigorously with egg beater Pour into hot greased popover pans Bake 15 minutes at 425 degrees hot oven reduce heat to 375 moderate oven and bake 30 minutes

Rice Bread

1 cup rice flour	1 tbsp sugar
3 tsp baking powder	½ tsp salt
2 tbsp bacon fat or oil	¾ cup water

Sift the dry ingredients Add water and fat Bake in a loaf pan in a moderate oven For greasing pans use only fat or oil as specified in the diet

Rye Rice Bread

1/3 cup rye flour	5 tsp baking powder
2/3 cup rice flour	2 tsp olive oil
½ tsp salt	1 cup water
6 tsp sugar	

Sift the dry ingredients together Add water and oil Bake in a loaf pan in a moderate oven for 40 minutes

Lima Bean Potato Cake and Cookies

6 tbsp lima bean flour	2/3 cup sugar
¾ cup potato flour	2½ tsp baking powder
5 tbsp shortening	½ tsp vanilla
½ cup water	½ tsp lemon extract
Few grains salt	Few drops yellow coloring

Sift dry ingredients cream fat and sugar add dry ingredients and water alternately to creamed mixture Add flavorings and coloring Put in greased muffin tins and bake in oven at 430 degrees for 30 minutes

Lima Bean Potato Muffins and Bread

2/3 cup potato flour	½ tsp salt
½ cup lima bean flour	4 tsp sugar
3 tsp baking powder	½ cup water
2 tbsp shortening	

Sift dry ingredients together Melt fat and add to water add slowly to dry ingredients Put in greased muffin tins and bake at 400 degrees for 20 minutes Serve hot Makes 10 small muffins

Lima Bean Soya Bean Bread

Substitute soya bean flour for potato in recipe for potato lima bread

Appendix 7

COMMON COSMETIC IRRITANTS AND ALLERGENS*

ngredients used in cosmetic manufacture reported cause allergic reactions

Substance	*Commonly found in*	*Symptoms*
Acetone	Nail polish removers	Peeling and splitting of the nails Dermatitis of the fingers
Almond oil	Cosmetic creams Lotions Perfumes Soaps	Rhinitis Dermatitis venenata
Alum	Astringent lotions Anhidrotics	Dermatitis venenata
Aluminum acetate Aluminum chloride Aluminum sulphate	Astringent lotions Anhidrotics Deodorants	Dermatitis venenata
Ammonium carbonate	Permanent wave solutions	Dermatitis of the scalp forehead and hands
Antimony compounds	Hair dyes	Dermatitis venenata
Arrow root	Dusting powder Dry shampoos	Rhinitis Conjunctivitis
Arsenic compounds	Hair tonics Hair dyes	Dermatitis venenata
Balsam of peru	Perfumes	Dermatitis venenata Rhinitis Perennial hay fever

*Courtesy Ar Ex Cosmetics Inc

Substance	Commonly found in	Symptoms
Barium sulphide	Depilatories	Dermatitis venenata
Benzaldehyde	Cosmetic creams Lotions	Dermatitis venenata
Betanaphthol	Hair dyes Skin peeling preparations	Dermatitis venenata
Bismuth compounds	Bleaching creams Freckle creams	Dermatitis venenata
Calcium sulfide	Depilatories	Dermatitis venenata
Cornstarch	Dusting powders Face powders	Conjunctivitis Rhinitis Perennial hay fever
Dibromfluorescein	Indelible lipsticks	Cheilitis often accompanied by respiratery symptoms and dermatitis, Gastrointestinal symptoms simulating colitis
Gum Arabic	Wave sets Rouge and powder compacts as a binder	Atopic coryza Atopic dermatitis Gastrointestinal distress Asthma
Gum Karaya	Wave sets Toothpaste Denture adhesive powder Hand lotions Rouge and powder compacts as a binder	Perennial hay fever Atopic coryza Atopic dermatitis Gastrointestinal distress Asthma
Gum Tragacanth	Wave sets Hand lotions Rouge and powder compacts as a binder	Atopic coryza Atopic dermatitis Gastrointestinal distress Asthma

Substance	Commonly found in	Symptoms
Lanolin	Cosmetic creams Lotions Shampoos Ointment bases	Dermatitis venenata
Lead compounds	Hair dyes	Dermatitis venenata
Lycopodium	Dusting powders	Rhinitis Perennial hay fever
Mercury compounds	Bleaching creams Freckle creams Hair tonics Medicated soaps	Dermatitis venenata
Methyl heptine carbonate	Perfumes Toilet waters Perfumed cosmetics	Rhinitis Perennial hay fever Asthma Dermatitis when comes in contact with the skin
Oil of bergamot Oil of cananga Oil of coriander Oil of geraniol Oil of heliotropine Oil of hydroxy-citronellal	Perfumes Toilet waters Perfumed cosmetics	Rhinitis Perennial hay fever Asthma Dermatitis when they come in contact with the skin
Oil of lavender Oil of lemon Oil of lemongrass Oil of linalool Oil of neroli Oil of orangepeel Oil of origanum Oil of orris Oil of ylang ylang		Photosensitivity
Oil of cassia (clove) Oil of peppermint Oil of spearmint Oil of wintergreen	Perfumes Toilet waters Perfumed cosmetics Toothpaste Toothpowder	Rhinitis Perennial hay fever Asthma Dermatitis when they come in contact with the skin

Substance	*Commonly found in*	*Symptoms*
Oil of citronella	Perfumes Toilet waters Perfumed cosmetics Mosquito repellant creams	Rhinitis Perennial hay fever Asthma Dermatitis when they come in contact with the skin
Orris root powder	Toothpaste Dry shampoos Sachets Formerly contained in most face powders but now only rarely used	Infantile eczema Perennial hay fever Rhinitis Conjunctivitis Asthma
Paraphenylenediamine	Hair dyes Eyebrow and eyelash dyes	Dermatitis venenata
Phenol	Hand lotions	Dermatitis venenata
Potassium carbonate Potassium sulphite	Permanent wave solutions	Dermatitis of the scalp, forehead, and hands
Pyrogallol	Hair dyes	Dermatitis venenata
Quinine sulphate	Hair tonics	Dermatitis venenata
Resorcinol	Hair tonics	Dermatitis venenata
Rice starch	Face powder Dusting powder	Conjunctivitis Rhinitis Perennial hay fever
Rosin	Hair lacquers	Dermatitis venenata
Salicylic acid	Deodorants Hair tonics	Dermatitis venenata
Sodium carbonate	Permanent wave solutions	Dermatitis of the scalp, forehead, and hands
Strontium sulfide	Depilatories	Dermatitis venenata

Substance	*Commonly found in*	*Symptoms*
Tetrabromfluorescein	Indelible lipsticks	Cheilitis, often accompanied by respiratory symptoms and dermatitis Gastrointestinal symptoms simulating colitis
Thioglycollic acid salts	Cold permanent wave preparations	Dermatitis venenata
Wheat starch	Dusting powders Face powders	Conjunctivitis Rhinitis Perennial hay fever
Zinc chloride Zinc sulphate	Astringent lotions	Dermatitis venenata

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